(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 February 2002 (21.02.2002)

PCT

(10) International Publication Number
WO 02/14321 A1

(51) International Patent Classification[7]: C07D 487/04, 513/04, A61K 31/425, 31/505

(21) International Application Number: PCT/US01/25175

(22) International Filing Date: 10 August 2001 (10.08.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/637,531 11 August 2000 (11.08.2000) US
60/301,340 26 June 2001 (26.06.2001) US

(71) Applicant *(for all designated States except US)*: **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA** [US/US]; 1111 Franklin Street, 12th Floor, Oakland, CA 94607-5200 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **COTTAM, Howard, B.** [US/US]; 1890 Lendee Drive, Escondido, CA 92025 (US). **LEONI, Lorenzo, M.** [CH/US]; 3908 Via Tranquilo, San Diego, CA 92122 (US). **CARSON, Dennis, A.** [US/US]; 14824 Vista del Oceano, Del Mar, CA 92014 (US). **BARCHECHATH, Sylvie** [US/US]; 39310 Towne Center Drive #80, La Jolla, CA 92093 (US).

(74) Agent: **VIKSNINS, Ann, S.**; Schwegman, Lundberg, Woessner & Kluth, P.O. Box 2938, Minneapolis, MN 55402 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/14321 A1

(54) Title: USE OF STAT-6 INHIBITORS AS THERAPEUTIC AGENTS

(57) Abstract: The present invention provides polycyclic imidazole derivatives useful to inhibit cancer or sensitize cancer cells to chemotherapeutic agents, radiation or other anti-cancer treatments.

USE OF STAT-6 INHIBITORS AS THERAPEUTIC AGENTS

Cross-Reference to Related Applications

This application claims priority of U.S. patent application Serial No. 09/637,531, filed August 11, 2000, and U.S. provisional patent application Serial No. 60/301,340, filed June 26, 2001, both of which are incorporated by reference herein.

BACKGROUND OF THE INVENTION

This invention was made with the assistance of the National Institutes of Health under Grant Nos. GM23200 and CA81534. The U.S. Government has certain rights in this invention.

The cytokines IL-4 and IL-13 interact with receptors on target B cells, and stimulate the production of IgE and other mediators of allergy. However, recent data indicate that IL-4/IL-13 signaling also (1) inhibits apoptosis in malignant B cells and other cancer cells, (2) prevents the rejection of tumors by the body, (3) promotes the survival of fibroblasts and therefore increases fibrosis, and (4) stimulates the differentiation of antigen-presenting cells.

The STAT4 and STAT6 genes encode transcription factors that when phosphorylated by Janus kinases are activated and transported to the nucleus where they regulate cytokine-induced gene expression. See, e.g., J. T. Ihle, Stem Cells Suppl., 1, 105 (1997); M. Heim, J. Recept. Signal. Transduction Res., 19, 75 (1999); K. S. Liu et al., Curr. Opin. Immunol., 10, 271 (1998). For example, STAT-6 is the common transcription factor for IL-4 and IL-13.

STAT4 and STAT6 are essential for the development of $CD4^+$ Th1 and Th2 development, respectively. Tumor immunologists have hypothesized that Th1 cells are critical in tumor immunity because they facilitate differentiation of $CD8^+$ T cells, which are potent anti-tumor effectors. S. Ostrand-Rosenberg et al., J. Immunol., 165, 6015 (2000) used $STAT4^{-/-}$ and $STAT6^{-/-}$ mice to test this

hypothesis. BALB/c and knockout mice were challenged in the mammary gland with the highly malignant and spontaneously metastatic BALB/c-derived 4T1 mammary carcinoma. Primary tumor growth and metastatic disease were reduced in STAT6$^{-/-}$ mice relative to BALB/c and STAT4$^{-/-}$ mice. Ab depletions demonstrated that the effect is mediated by CD8^{+} T cells, and immunized STAT6$^{-/-}$ mice had higher levels of 4T1-specific CTL than BALB/c or STAT4$^{-/-}$ mice. Th1 or Th2 cells were not involved, because CD4 depletion did not diminish the anti-tumor effect. Therefore, deletion of the STAT6 gene facilitates development of potent anti-tumor immunity via a CD4^{+}-independent pathway.

Sumitumo Pharmaceutical Co. (published Japanese Patent Application, JP 1997/000288026) discloses certain imidazo [2,1-b]thiazole derivatives that are capable of inhibiting STAT-6. The compounds are disclosed to be useful for the treatment and prevention of allergic diseases and parasitic infectious diseases. However, a continuing need exists for small molecules that can inhibit STAT-6 and thus, inhibit IL-4 and IL-13 signal transduction. Such compounds can be used therapeutically as discussed hereinbelow.

In addition, there is a need for novel, potent, and selective agents to prevent detrimental effects upon cells due to DNA damage, such as caused by chemotherapy, radiation, ischemic event, including ischemia-reperfusion injury and organ transplantation, and the like. There is also a need for pharmacological tools for the further study of the physiological processes associated with intracellular DNA damage.

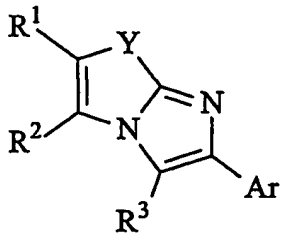
p53, the product of the p53 tumor suppressor gene, is a multifunctional tumor suppressor protein, involved in the negative control of cell growth. In response to a variety of stressors, p53 induces growth arrest or apoptosis, thereby eliminating damaged and potentially dangerous cells. T. M. Gottleib et al., Biochim. Biophys. Acta, 1287, 77 (1996). Mutations in the p53 gene are frequently associated with the metastatic stage of tumor progression, and lack of functional p53 is accompanied by rapid tumor progression, resistance to anti-cancer therapy and increased tumor angiogenesis. See, e.g., A. J. Levine et al.,

Br. J. Cancer, 69, 409 (1994); R. J. Steele et al., Br. J. Surg., 85, 1460 (1998); C. Cordon-Cardo et al., Surg. Oncol., 13, 319 (1997). p53 deficiency in mice is associated with a high frequency of spontaneous cancers. L. A. Donehower et al., Nature, 356, 215 (1992); T. Jacks et al., Curr. Biol., 4, 1 (1994). On the basis of these reports, the inactivation of p53 was viewed as an unfavorable event, and it has been speculated that cancer can be inhibited by restoration of p53 function.

A continuing need exists for compounds that can protect mammalian cells from the damaging effects of chemotherapy and irradiation, or in other situations in which it is desirable to protect tissue from the consequences of clinical or environmental stress.

SUMMARY OF THE INVENTION

The present invention provides compounds that act to inhibit the activity of STAT-6 in mammalian cells, and a method to effectively inhibit signal transduction through the IL-4 and IL-13 pathways, *in vitro* or *in vivo*, in the cells of a mammal, such as a human, subject to pathology that is ameliorated by such inhibition. Accordingly, there is provided a method of suppression comprising administering to a mammal in need of said suppression an effective amount of a compound of formula (I):



(I)

wherein R^1, R^2 and R^3 are independently hydrogen, halo, hydroxy, cyano, $N(R_a)(R_b)$, $S(R_a)$, NO_2, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_7)$alkanoyl, $(C_2\text{-}C_7)$alkanoyloxy, or $(C_3\text{-}C_7)$cycloalkyl or R^1 and R^2 taken together are benzo, optionally substituted by R^1, or are $(C_3\text{-}C_5)$alkylene or methylenedioxy; wherein R_a and R_b are each independently hydrogen, $(C_1\text{-}C_3)$alkyl, $(C_2\text{-}C_4)$alkanoyl, phenyl, benzyl, or phenethyl; or R_a and

R_b together with the nitrogen to which they are attached are a 5-6 membered heterocyclic ring, preferably a pyrrolidino, piperidino or morpholino ring;

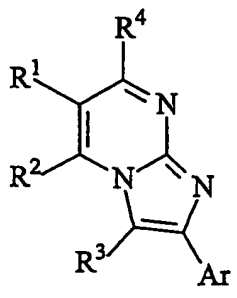
Ar is aryl, heteroaryl, or a 5-6 membered heterocyclic ring, preferably comprising 1-3 $N(R_a)$, nonperoxide O or S atoms, such as a pyrrolidino, piperidino or morpholino ring, optionally substituted with 1-5, preferably 1-2, halo, CF_3, hydroxy, CN, $N(R_a)(R_b)$, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_2-C_7)alkanoyl, (C_2-C_7)alkanoyloxy, (C_3-C_7)cycloalkyl, (C_2-C_6)alkanoyl, (C_2-C_6)alkenyl, or phenyl;

Y is oxy (–O–), $S(O)_{0-2}$, Se, $C(R^1)(R^3)$, $N(R_a)$, or –P–;

or a pharmaceutically acceptable salt thereof.

Preferably, Ar is not substituted with halo or alkoxy. Preferably, Ar is heteroaryl or a heterocyclic ring. Preferably, R^1 and R^2 are not benzo or (C_3-C_5)alkylidenyl when Ar is aryl, e.g., is phenyl or napthyl. Novel compounds of formula (I) are also within the scope of the present invention, e.g., preferably Y is -O-, -Se-, $C(R_1)(R_3)$ or P. Preferably, Ar is heteroaryl. Preferably, Ar is substituted with CN, (C_2-C_7)alkanoyl), (C_2-C_7)alkanoyloxy, (C_3-C_7)cycloalkyl, (C_2-C_6)alkenyl or combinations thereof. Preferably, R^1, R^2 and R^3 are independently, OH, CN $(N(R_a)(R_b)$, $S(R_a)$, NO_2, (C_2-C_7)alkanoyl, or (C_2-C_7)alkanoyloxyl.

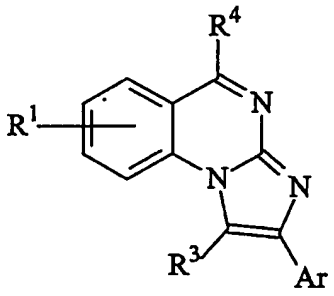
The present method also provides a therapeutic method comprising suppressing STAT-6 or the IL-4/IL-13 pathways in mammalian cells *in vitro* or *in vivo*, and thus treating a pathological condition ameliorated by said suppression, comprising administering to a mammal in need of said suppression an effective amount of a compound of formula (II):



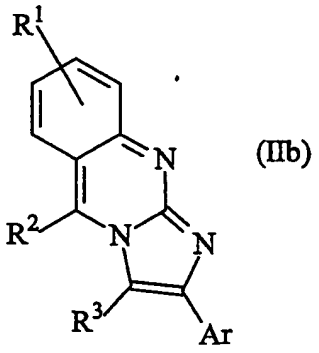
(II)

wherein R_1, R_2 and R_3 as well as Ar are defined as above; R_4 is the same as, but independent from, R_1, R_2 and R_3. R_4 in combination with R_1 can also be benzo, C_3-C_5 alkylidene or methylenedioxy. These compounds are imidazo[1,2-a]-quinazolines.

Compounds of formula (II) also include (IIa) and (IIb):



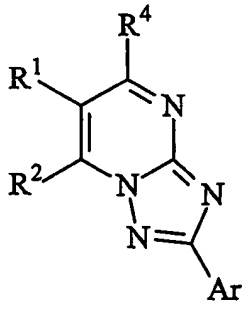
(IIa) and



(IIb)

wherein R_1, R_2, R_3 and R_4 are as defined herein. Novel compounds of formulae II, IIa and IIb are also within the scope of the invention. Preferably, R_4 is not OH in IIa or IIb, e.g., where R_1 and R_2 or R_1 and R_4 are benzo. In compounds of formula II, R_1 and R_2 are preferably not benzo when Ar is phenyl.

The present invention also includes compounds of formula III:



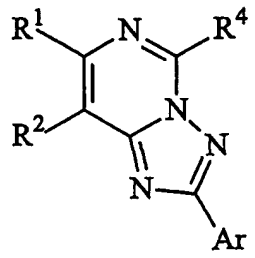
(III)

wherein R_1, R_2 and R_4, as well as Ar are defined as herein, for formula (I).

Also included within the invention are methods of using compounds of formula III in amounts effective to suppress STAT-6 or the IL-4/IL-13 pathways

in mammalian cells, and thus to provide treatment for a mammal afflicted by a pathology ameliorated by said suppression.

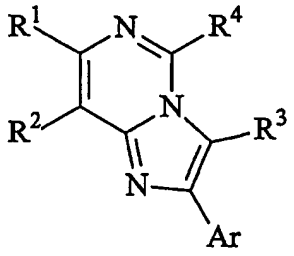
Compounds of formula (IV) are also included in the invention:



(IV)

wherein R_1, R_2 and R_4, as well as Ar are defined as above, for formula (II), as well as methods for their use to treat conditions ameliorated by a suppression of STAT-6 or by inhibition of signal transduction through the IL-4/IL-13 pathways in mammalian cells *in vitro* or *in vivo*. Preferably, R_1 and R_2 are not benzo when R_4 is H or OH.

Compounds of formula (V) are also included in the invention:



(V)

wherein R_1, R_2, R_3 and R_4 as well as Ar are defined as above, for formula (II), as well as methods for their use as discussed above. Preferably, Ar is not 4-methoxyphenyl when R_1 and R_2 are benzo and R_4 is H.

Compounds of formulae (I)-(V) are small molecule antagonists of IL-4/IL-13 signal transduction in mammalian cells *in vitro* and *in vivo*. These

molecules can inhibit the survival of malignant B cells and sensitize them to other chemotherapeutic agents, but are relatively nontoxic to normal lymphocytes. Antibodies to IL-4 and IL-13 receptors and to other receptors are in clinical trials. However, IL-4 and IL-13 have redundant activities, and thus blocking only one of them is insufficient in many instances. Preferred compounds (I)-(IV) can block both IL-4 and IL-13 signaling. They may act by inhibiting expression of the STAT-6 gene, and thus by inhibiting STAT-6, the common transcription factor for IL-4 and IL-13. They can be useful to treat cancer, fibrotic diseases and inflammatory diseases.

More specifically, compounds (I)-(V) may be useful for:

1. Treatment of leukemia, lymphoma, and other cancers expressing IL-4 and/or IL-13 receptors (e.g., gliomas and head and neck cancers).
2. Sensitization of cancer cells to monoclonal antibodies and chemotherapeutic agents.
3. Use in vaccines against cancer and viral diseases to increase cytotoxic T cell responses.
4. Treatment of proliferative fibrotic diseases, such as rheumatoid arthritis, pulmonary fibrosis, liver cirrhosis, and chronic kidney diseases.

IL-4 and IL-13 are known to be essential for asthma and allergies. T. Akimoto et al., J. Exp. Med., 182, 1537 (1998) report that STAT-6 deficient mice, which cannot respond to IL-4/IL-13, also do not develop allergic asthma.

M. Dancescu et al., J. Exp. Med., 176, 1319 (1992) and U. Kapp, J. Exp. Med., 189, 1939 (1999) report that IL-4 and IL-13 are survival factors for malignant cells in chronic lymphocytic leukemia and Hodgkin's disease (a form of lymphoma). Thus, the present compounds should be useful for treatment of these diseases.

K. Kawakami et al., Cancer Res., 60, 2981 (2000) reports the expression of IL-4 receptors in head and neck cancer, melanoma, breast cancer, ovary cancer, neuroblastomas, renal carcinomas. The present compounds thus can be useful for treatment of these cancers.

M. Terabe et al., Nature/Immunol., 1, 516 (2000) and S. Ostrand-Rosenberg, cited above, report the remarkable finding that lack of STAT-6 signaling promoters immune rejection of cancers. Thus, the claimed compounds can be used in cancer vaccines and/or with monoclonal antibodies to enhance their immunologic effects.

U. Muller-Ladner et al., J. Immunol., 164, 3894 (2000) reported that the IL-4 pathway is active in the fibroblasts that show unrestrained growth in the joints of patients with rheumatoid arthritis. Similar outgrowth of fibroblasts is seen in pulmonary fibrosis, cirrhosis, renal diseases, scleroderma. The present compounds can be useful in all these conditions.

The invention also provides pharmaceutical compositions comprising novel compounds of formula (I)-(V), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

The invention also provides novel compounds of formula (I), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier. Such compounds can be represented by compounds of formula (I), with the proviso that when Y is S, Ar is not phenyl (C_6H_5).

Additionally, the invention provides a therapeutic method for preventing or treating a pathological condition or symptom in a mammal, such as a human, wherein the activity of STAT-6 or IL-4/IL-13-mediated signal transduction is implicated and antagonism or suppression of their action is desired, comprising administering to a mammal in need of such therapy, an effective amount of one or more compounds of formula (I)-(V), or a pharmaceutically acceptable salt thereof. Such pathological conditions or symptoms include treatment of cancers expressing IL-4 and/or IL-13 receptors, sensitization of cancer cells to chemotherapy or radiation, increasing T_c cell responses and the treatment of proliferative fibrotic disease.

The invention provides a compound of formula (I)-(V) for use in medical therapy as well as the use of a compound of formula (I)-(V) for the manufacture of a medicament for the treatment of a pathological condition or symptom in a mammal, such as a human, which is associated with STAT-6 activation,

activation of the IL-4 and/or IL-13 pathways, or p53-induced cellular damage, i.e., with unwanted apoptosis.

The invention also includes a method for binding a compound of formula (I)-(V) to cells and biomolecules comprising IL-4 and/or IL-13 receptors, *in vivo* or *in vitro*, comprising contacting said cells or biomolecules with an amount of a compound of formula (I)-(V) effective to bind to said receptors. Cells or biomolecules comprising ligand-bound IL-4/IL-13 receptor sites can be used to measure the selectivity of test compounds for specific receptor subtypes, or can be used as a tool to identify potential therapeutic agents for the treatment of diseases or conditions associated with IL-4/IL-13 pathway activation, by contacting said agents with said ligand-receptor complexes, and measuring the extent of displacement of the ligand and/or binding of the agent, by methods known to the art.

In another embodiment, the present invention provides a compound of formula (I)-(V) that act to suppress p53 activity in mammalian cells, and a method to effectively suppress p53 activity in the cells of a mammal subject to a stress or pathology that is ameliorated by such suppression. Accordingly, there is provided a method of p53 suppression comprising administering to a mammal in need of said suppression an effective amount of a compound of formula (I)-(V).

The invention also provides novel p53 suppressor compounds, as well as pharmaceutical compositions comprising novel compounds of formula (I)-(V), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier. Such compounds can be represented by compounds of formula (I), with the proviso that when Y is S, Ar is not phenyl (C_6H_5).

Additionally, the invention provides a therapeutic method for preventing or treating a pathological condition or symptom in a mammal, such as a human, wherein the activity of p53 is implicated and antagonism or suppression of its action is desired, comprising administering to a mammal in need of such therapy, an effective amount of a compound of formula (I)-(V), or a pharmaceutically

acceptable salt thereof. Such pathological conditions or symptoms include blocking, moderating or reversing the deleterious effects of chemotherapeutic agents, particularly those which damage DNA; radiation, particularly radiation therapy (gamma-, beta- or UV-radiation), ischemic event, including stroke, infarct, ischemia-reperfusion injury and ischemia due to organ, tissue or cell transplantation; environmental pollution or contamination and the like.

The invention also includes a method for binding a compound of formula (I) to cells and biomolecules comprising p53 receptors, *in vivo* or *in vitro*, comprising contacting said cells or biomolecules with an amount of a compound of formula (I) effective to bind to said receptors. Cells or biomolecules comprising ligand-bound p53 receptor sites can be used to measure the selectivity of test compounds for specific receptor subtypes, or can be used as a tool to identify potential therapeutic agents for the treatment of diseases or conditions associated with p53 activation, by contacting said agents with said ligand-receptor complexes, and measuring the extent of displacement of the ligand and/or binding of the agent, by methods known to the art.

As used herein, the term "p53" or "p53 activity" refers to p53 protein. The invention is believed to work by temporarily suppressing expression of the p53 gene and/or activity of p53 protein.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts the effects of IBT and PFT-α on B-CLL viability.

Figure 2 depicts the protective effect of IBT against spontaneous apoptosis and against fludarabine-induced apoptosis.

Figure 3 shows the ability of the various compounds to block the expression of a STAT-6 dependent reporter gene.

Figure 4 shows the ability of compounds of the invention to reduce the survival of malignant B cells from a patient with chronic lymphocytic leukemia maintained in tissue culture for 72 hours.

Figure 5 shows the structures of compounds numbered in Figures 3-4. Compound 1 is IBT (control).

DETAILED DESCRIPTION

The following definitions are used, unless otherwise described: halo is fluoro, chloro, bromo, or iodo. Alkyl, alkoxy, alkenyl, alkynyl, etc. denote both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Heteroaryl encompasses a radical attached via a ring nitrogen or carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(X) wherein X is absent or is H, O, $(C_1$-$C_4)$alkyl, phenyl or benzyl. Heteroaryl also includes a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms, particularly a benzo-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto. Preferred heteroaryls include pyridin-4-yl and thiophen-2-yl. The term "heterocyclic ring" "heterocycle," or "heterocycyl," is defined as above for formula (I).

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may also exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically active, polymorphic, or steroisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine STAT-6 suppression activity using the standard tests described herein, or using other similar tests which are well known in the art. When R^4 is OH, enol or keto forms of compounds (II)-(V) are also within the scope of the invention, wherein the adjacent N may be replaced by $N(R_a)$.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically, (C_1-C_6)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl; (C_3-C_7)cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; the term cycloalkyl includes (cycloalkyl)alkyl of the designated number of carbon atoms; (C_3-C_5)cycloalkyl(C_2-C_4)alkyl can be cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 2-cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl, or 2-cyclohexylmethyl; (C_1-C_6)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, or hexyloxy; (C_2-C_6)alkenyl can be vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, or 5-hexenyl; (C_2-C_6)alkynyl can be ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, or 5-hexynyl; (C_2-C_7)alkanoyl can be acetyl, propanoyl or butanoyl; halo(C_1-C_6)alkyl can be iodomethyl, bromomethyl, chloromethyl, fluoromethyl, trifluoromethyl, 2-chloroethyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, or pentafluoroethyl; hydroxy(C_1-C_6)alkyl can be hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxybutyl, 4-hydroxybutyl, 1-hydroxypentyl, 5-hydroxypentyl, 1-hydroxyhexyl, or 6-hydroxyhexyl; (C_1-C_6)alkoxycarbonyl can be methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, or hexyloxycarbonyl; (C_1-C_6)alkylthio can be methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, pentylthio, or hexylthio; (C_2-C_6)alkanoyloxy can be acetoxy, propanoyloxy, butanoyloxy, isobutanoyloxy, pentanoyloxy, or hexanoyloxy; aryl can be phenyl, indenyl, or naphthyl; and heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazoyl, isoxazoyl, thiazolyl, isothiazoyl, pyrazolyl, pyrrolyl, pyrazinyl,

tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

A specific value for R^1 and R^2 is hydroxy, cyano, $N(R_a)(R_b)$, $S(R_a)$, NO_2, $(C_2\text{-}C_7)$alkanoyl, or $(C_2\text{-}C_7)$alkanoyloxy

A specific value for R^1 and R^2 together is butylene or benzo.

A specific value for R^1 and R^4 together is butylene or benzo.

A specific value for R^3 is H.

A specific value for R^4 is H.

A specific value for Ar is aryl or heteroaryl, optionally substituted with 1-5, preferably 1-2, halo, CF_3, hydroxy, CN, $N(R_a)(R_b)$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_7)$alkanoyl, $(C_2\text{-}C_7)$alkanoyloxy, $(C_3\text{-}C_7)$cycloalkyl, $(C_2\text{-}C_6)$alkanoyl, $(C_2\text{-}C_6)$alkenyl, or phenyl.

A specific value for Ar is heteroaryl or phenyl substituted with CN, $(C_2\text{-}C_7)$alkanoyl, $(C_2\text{-}C_7)$alkanolyoxy, $(C_2\text{-}C_7)$cycloalkyl or $(C_2\text{-}C_6)$alkenyl.

A specific value for Ar is phenyl, 2, 3 or 4-pyridyl or 2-thienyl; pyrrolidino, piperidino or morpholino.

A more specific value for Ar is phenyl, 4-pyridyl or 2-thienyl.

A specific value for Y is oxy (–O–), $S(O)_{0\text{-}2}$, $C(R^1)(R^3)$, $N(R_a)$, or –P–.

A specific value for Y is S, O, $N(R_a)$, or –P–.

A specific value for Y is P, Se, SO, SO_2 or $C(R_1)(R_3)$.

A specific value for Y is P, Se, S(O) or SO_2.

A more specific value for Y is S, O, or NH_2,

A specific value for $N(R_a)(R_b)$ is amino.

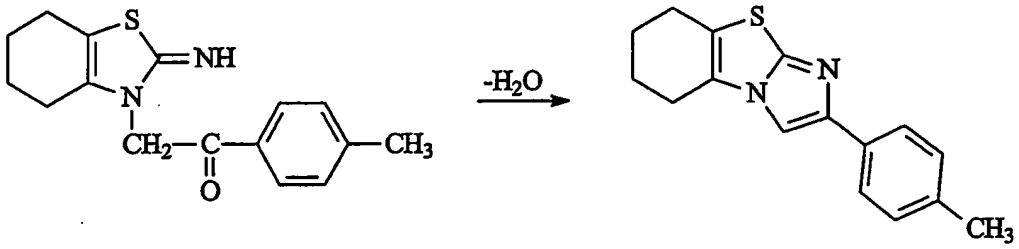
A specific value for $N(R_a)(R_b)$ is pyrrolidino, piperidino or morpholino.

A specific value for halo is Br or F.

Processes for preparing compounds of formula (I) are provided as further embodiments of the invention and are illustrated by the procedures disclosed below in which the meanings of the generic radicals are as given above unless otherwise qualified.

Intermediates useful for preparing compounds of formula (I), are also within the scope of the present invention.

The present invention is based on the discovery that PFT-α is both cytotoxic to mammalian cells and unstable in aqueous solution under *in vivo* conditions. PFT-α undergoes spontaneous ring closure in protic solvents, such as alkanols, to form the imidazo[2,1-b]benzothiazole derivative, abbreviated IBT, as shown in Scheme 1.

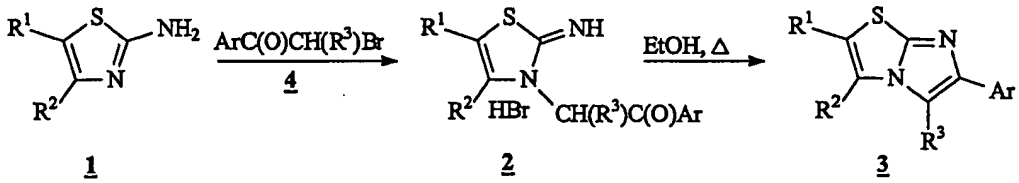


PFTα IBT

Scheme 1

Biological evaluation, described below, demonstrated that IBT is actually responsible for the observed p53 inhibition observed by Komarov et al. (Science, 285, 1733 (1999)). Thus, since IBT and compounds of formula (I) are expected to be both less toxic and more stable than imino compounds such as PFT-α, they are desirable agents for protection of mammalian cells against a wide variety of stressors, including therapeutic agents, and clinical and environmental trauma.

Compounds of formula (I) can be readily prepared as disclosed by Singh et al., Indian J. Chem., 7, 997 (1996), as shown in Scheme 2.

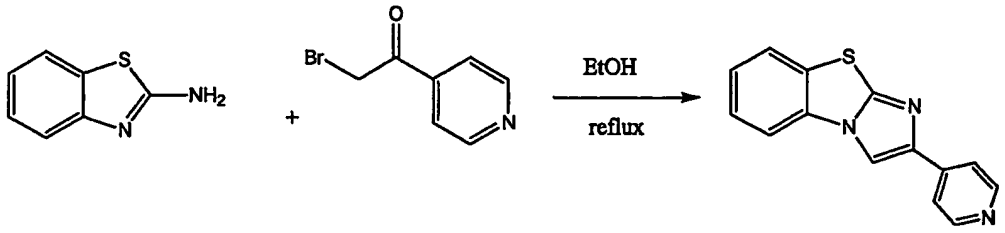


1 2 3

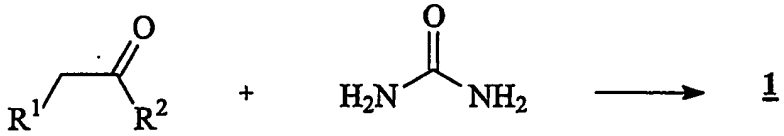
Scheme 2

In Scheme 2, a suitable 2-aminobenzothiazole derivative is reacted with an alpha-haloketone in refluxing ethanol resulting in alkylation and ring closure

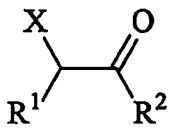
in one single step. An example for the pyridinyl-substituted derivative is given below:



In Scheme 2, the reaction of 1 and 4 can be carried out simply by combining the compounds in a suitable aprotic solvent such as benzene. See, I. Soldabols et al., Khim. Pharm. Zh., 1, 17 (1967). The conversion of 1 → 3 can also be accomplished in one step by refluxing 1 and the phenacyl bromide 4 in ethanol. Singh et al. used starting materials wherein R^1 and R^2 together are $-(CH_2)_4-$ or $-CH(CH_3)-(CH_2)_3-$ and Ar is substituted phenyl. Recently, Sumitomo Pharmaceutical Co. Ltd. (Japanese Pat. No. 11-29475) (1999)) disclosed the preparation of certain compounds of formula 2, wherein R^3 is H and Ar is substituted phenyl, and Japanese Pat. No. 11-106340 (1999) disclosed the preparation of certain compounds of formula 3 wherein Ar is substituted phenyl or napthyl and R^1 and R^2 can be, *inter alia*, H, alkylene or benzo. Compounds of formula 1 were prepared according to Scheme 3.



or



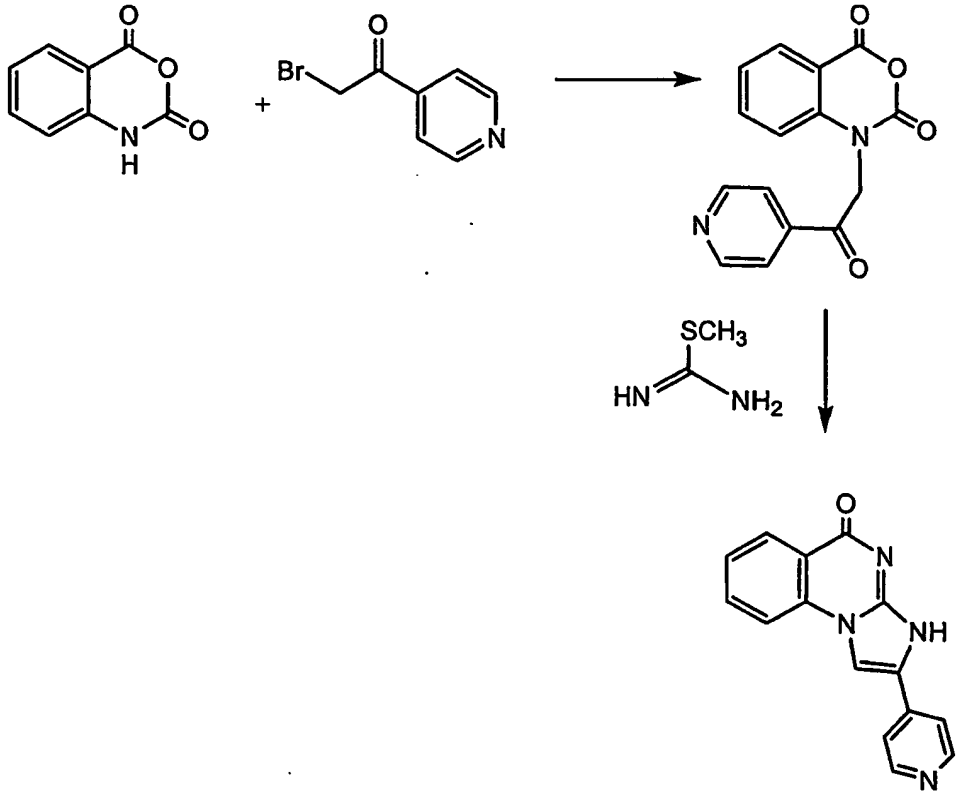
Scheme 3

The compounds of formula (I) are disclosed to be useful for "the treatment and prevention of allergic disease and parasitic infectious diseases, or the like."

Certain of the compounds of formula (I) are useful as intermediates to prepare other compounds of formula (I), as would be recognized by the art.

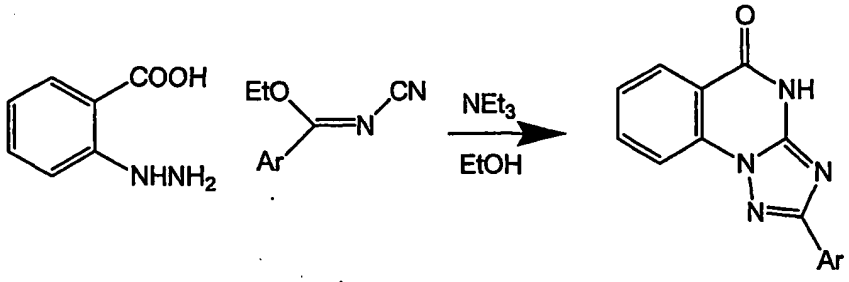
Compounds of formulae (II)-(V) can be prepared as generally described in PCT/WO97/42192; U.S. Pat. No. 4,020,062, Armianianskii Khim. Zhuv., 43, 245 (1990); Coppola et al., J. Org. Chem., 41, 825 (1976) (II); M. A. Likhale et al., J. Ind. Chem. Soc., 69, 667 (1992); K. T. Potts et al., J. Org. Chem., 35, 3448 (1970); J. E. Francis et al., J. Med. Chem., 34, 281, 2899 (1991) (IV) and A. Guieflier, J. Het. Chem., 27, 421 (1990) (V).

A general method for preparation of imidazo[1,2-a]quinazolines of formula (II) is found in Coppola, et al., wherein a functionalized isatoic anhydride is first alkylated with the alpha-haloketone and then condensed with a suitable thiopseudourea, as shown below for a pyridinyl derivative:

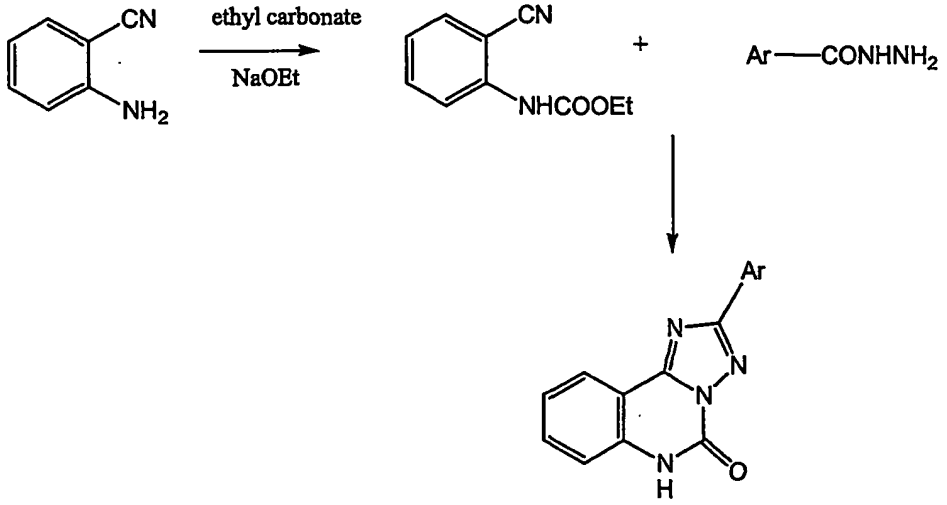


A procedure reported by R. Heckendorn et al., Helv. Chim. Acta, 63, 1 (1980) can be used to prepare the 2-aryl-substituted

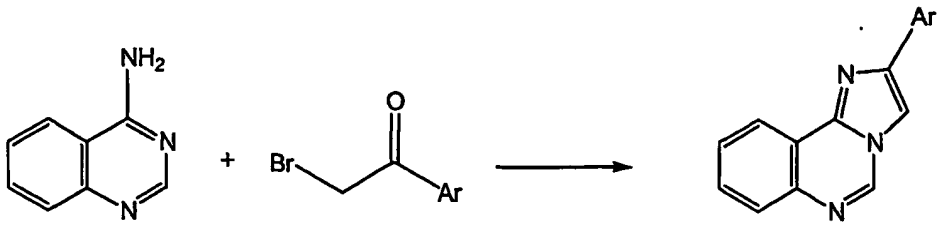
1,2,4-triazolo[1,5-a]quinazolines wherein a 2-hydrazinobenzoic acid is condensed with an appropriate N-cyanoimidate ester as shown below:



A suitable procedure by Francis, et al., cited above, is used to obtain aryl substituted 1,2,4-triazolo[1,5-c]quinazolines of formula (IV), wherein an appropriate anthranilonitrile is converted to the corresponding carbamate by reaction of the nitrile with ethyl carbonate in the presence of sodium ethoxide, followed by condensation with a suitable aryl carbohydrazide or heteroaryl carbohydrazide as shown below:



Imidazo[1,2-c]quinazolines of formula (V) may be prepared according to the procedure outlined by Gueffier, et al., wherein a 4-aminoquinazoline is reacted with a bromomethyl aryl ketone in refluxing ethanol. Heteroaryl ketones may also be used as shown below for a pyridinyl derivative:



In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example, by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example, calcium) salts of carboxylic acids can also be made.

The compounds of formula (I)-(V) can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human cancer patient, in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches,

capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glycerol esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelation.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers

include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of formula (I)-(V) to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of formula (I)-(V) can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

Generally, the concentration of the compound(s) of formula (I)-(V) in a liquid composition, such as a lotion, will be from about 0.1-25 wt %, preferably from about 0.5-10 wt %. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt %, preferably about 0.5-2.5 wt %.

The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 0.5 to about 100 mg/kg, e.g., from about 10 to about 75 mg/kg of body weight per day, such as 3 to about 50 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day.

The compound is conveniently administered in unit dosage form, for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form.

Ideally, the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.5 to about 75 μM, preferably, about 1 to 50 μM, most preferably, about 2 to about 30 μM. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1-100 mg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the active ingredient(s).

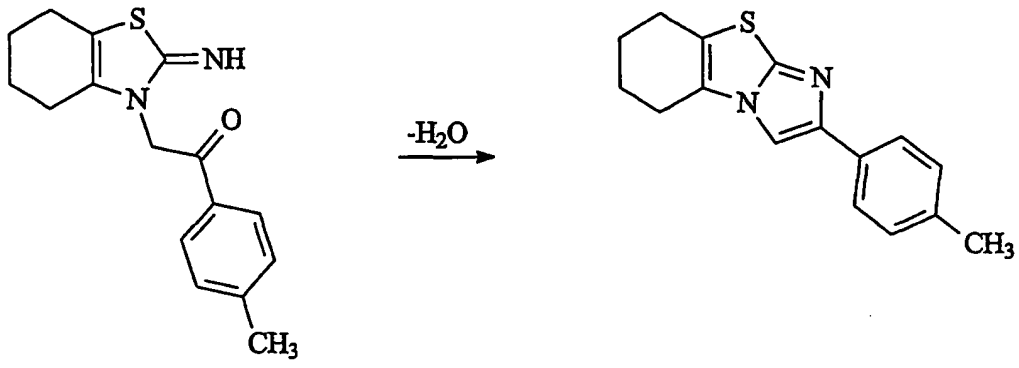
The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations, such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

The ability of a compound of the invention to act as a suppressor of p53 activity may be determined using pharmacological models which are well known to the art, e.g., as disclosed below.

The invention will now be illustrated by the following non-limiting Examples.

EXAMPLE 1

A. Ring-closure of PFT-α



PFT-α IBT

The preparation of PFT-α was accomplished as shown in Scheme 1 by reacting 4-methyl-2-bromoacetophenone with 2-amino-4,5,6,7-tetrahydrobenzothiazole. Upon recrystallization of the PFT-α from isopropyl alcohol, it was noticed that PFT-α readily ring-closed completely to the imidazo[2,1-b]benzothiazole (IBT). Therefore, a subsequent investigation was undertaken to study the propensity of PFT-α to ring-close in protic solvents. Initial results indicated that PFT-α begins cyclizing at room temperature immediately upon dissolution in protic solvents. Thus, PFT-α was dissolved in DMSO and water dilutions were made from this stock. Reversed phase HPLC analysis of the solution at 25°C over time gave results as shown in Table 1.

Table 1

Time (h)	% cyclized to IBT
0	5
12	47
24	69
48	92

In addition, NMR studies were used to confirm the structure of the known IBT and a time course in DMSO-d6 also showed spontaneous conversion of PFT-α to IBT, as judged by the appearance of a new aromatic proton signal at δ 8.50 ppm in the proton spectrum corresponding to the C_3H proton.

B. 2-(Pyridin-4-yl)imidazo[2,1-b]benzothiazole

A mixture of 2-aminobenzothiazole (0.01 mol) and 4-bromoacetylpyridine (0.01 mol) in anhydrous ethanol (100 mL) is refluxed for 5 hours. The reaction mixture is evaporated to dryness in vacuo and the residue is slurried in ice water. The resulting solid is filtered and dried to provide the title compound as the HBr salt in 60% yield.

C. 2-(Pyridin-4-yl)imidazo[1,2-a]quinazolin-9-one

Isatoic anhydride (0.01 mol) is treated with sodium hydride (0.012 mol) in dry dimethylacetamide (50 mL) at room temperature for 20 min. and then 4-bromoacetyl-pyridine (0.01 mol) is added and the mixture is stirred at 80 °C for 2 hours. The mixture is cooled and poured into cold, aqueous sodium carbonate (500 mL, saturated) and extracted with ethyl acetate (3 x 200 mL). The organic layer is dried over magnesium sulfate and evaporated to yield the crude alkylated isatoic anhydride which is used directly without further purification for the ring closure procedure. Thus, this ketone intermediate is suspended in acetonitrile (100 mL) containing methyl-2-thiopseudourea (0.012 mol) and sodium carbonate (0.012 mol) and the mixture is refluxed for 30 min. The solvent is then removed in vacuo and replaced with dichloromethane (100 mL). The insoluble salts are filtered off and washed with additional solvent, and the filtrate is evaporated to dryness and diglyme (50 mL) is added to the residue. After addition of one pellet of sodium hydroxide to catalyze the reaction, the mixture is refluxed for 2 hours. Upon cooling, a precipitate forms which is filtered, washed with a small amount of ethyl acetate and recrystallized from methanol or dichloromethane to yield the title compound.

D. 2-(p-Methylphenyl)[1,2,4]-triazolo[1,5-a]quinazolin-5-*4H*-one

To a cooled solution (0 °C) of N-cyanoarylethylimidate in absolute alcohol (75 mmol in 100 mL EtOH) is added dropwise triethylamine (225 mmol) over 30 min. and then 75 mmol of 2-hydrazinobenzoic acid hydrochloride is added portionwise keeping the temperature below 3°C. The mixture is then allowed to warm slowly to room temperature and is stirred overnight. The resulting mixture is cooled and neutralized with conc. HCl and warmed for 3 hours at 80°C with stirring. The reaction mixture is diluted with water and cooled to 5°C. The resulting solid product which separates is filtered off, washed with cold water, then ether and dried to yield the title compound.

E. 2-(Pyridin-4-yl)imidazo[1,2-c]quinazoline

A mixture of 4-aminoquinazoline (0.01 mol) and 4-bromoacetylpyridine (0.01 mol) in anhydrous ethanol (100 mL) is refluxed for 5 hours. The reaction mixture is evaporated to dryness in vacuo and the residue is slurried in ice water. The resulting solid is filtered and dried to provide the title compound as the HBr salt.

F. 2-(Pyridin-4-yl)1,2,4-triazolo[1,5-c]quinazolin-5(6H)-one

A mixture of the carbamate of anthranilonitrile (prepared by reacting anthranilonitrile (0.21 mol) with ethyl carbonate (250 mL) in absolute ethanol (500 mL) containing sodium ethoxide, 1.67 mol) is reacted with 4-pyridinecarbohydrazide (one to one equivalence, 55 mmol each) in 2-ethoxyethanol (185 mL) containing tri-n-propylamine (7.4 mL) by heating at reflux for 16 h, cooling, and treating with water gradually to promote crystallization. After overnight refrigeration, the solid product is collected and recrystallized from ethanol.

EXAMPLE 2

Effect of the p53 Inhibitory Compounds on B-CLL Viability

The malignant lymphocytes from two patients with chronic lymphocytic leukemia [CLL] were isolated by ficoll-hypaque sedimentation and suspended at a density of 1 million cells per milliliter in RPMI 1640 medium supplemented with 10% fetal bovine serum. Two hundred microliter aliquots of cells were

dispersed in the wells of culture plates containing the indicated final concentrations of either PFT-α ("PFT-open") or IBT (PFT-closed). After 3 days culture, viable cells were enumerated by fluorescence-activated cell sorting [FACS] after staining with propidium iodide [PI]. Viable cells excluded the dye [open circles]. In addition, cell metabolism was assessed by the ability of the cells to exclude the tetrazolium dye MTT [closed squares]. As shown in Figure 1, the PFT-open dose-dependently reduced CLL survival, whereas PFT-closed [i.e., IBT] was non-toxic at concentrations up to 100 micromolar.

EXAMPLE 3

Protection Against Spontaneous Apoptosis and Apoptosis Induced by the Anti-metabolite Fludarabine

Chronic lymphocytic leukemia [CLL] cells were cultured for 3 days as described in Example 2. Some of the cultures were supplemented with one micromolar of PFT-open or PFT-closed, as indicated. In the experiment shown in the bottom panel of Figure 2, some of the cultures also contained the cytotoxic adenine nucleoside analog fludarabine [abbreviated F-AraA]. Fludarabine is the first line treatment for CLL, and the toxicity of the drug is dependent upon the p53 pathway. To assess healthy, viable cells, staining was done with both PI, as indicated in Example 2, and with the mitochondrial dye DiOC6. Cells that were both PI negative and DIOC6 high were enumerated by FACS. While PFT-α and IBT exhibited nearly equivalent effects on untreated CLL cells, IBT exerted less protective effects when combined with CLL cells treated with F-AraA than did PFT-α.

EXAMPLE 4

Screening of compounds of formula (I) for inhibition of IL-4 transcriptional activity

The BEAS-2B human airway epithelial cells were transiently transfected with the human 12/15-lipoxygenase promoter/luciferase reporter gene. Cells were then incubated with the IBT analogs (Fig. 5) at 10 μM for 1 hour, followed

by IL-4 (10 ng/ml). After 16 hours, luciferase was measured using a chemiluminometer. The STAT-6 induction was normalized using the B-gal results as "background." The viability of the treated cells was visually verified at the end of the incubation, and found to be >95%. Results shown in Figure 3 are the mean of duplicate measurements.

EXAMPLE 5

Sensitization of CLL cells to apoptosis by IL-4/IL-13 antagonists

Chronic lymphocytic leukemia (CLL) cells were isolated from whole blood of patients, cultured in RPMI-1640 supplemented with 10% FB. CLL cells were pre-incubated for 1 hour with the indicated analogs (Fig. 5) at 1 μM and exposed for 24 hours to the nucleoside analogs Fludarabine (Fludara) and Cladribine (2 CdA) at 1 and 10 μM. Cells were then incubated for 10 minutes in growing medium with 5 μg/ml Propidium iodide and 40 nM $DiOC_6$ and analyzed by flow cytometry. Viable cells (Y axis) and high $DiOC_6$ (FL-1) and low PI (FL-3) fluorescence.

EXAMPLE 6

Preparation of Pharmaceutical Dosage Forms

The following illustrate representative pharmaceutical dosage forms, containing a compound of formula (I)-(V), for therapeutic or prophylactic use in humans.

(i) Table 1	mg/tablet
Compound of Formula (I)-(V)	100.0
Lactose	77.5
Povidone	15.0
Croscarmellose sodium	12.0
Microcrystalline cellulose	92.5
Magnesium stearate	3.0
	300.0

(ii) Table 2	mg/tablet
Compound of Formula (I)-(V)	20.0
Microcrystalline cellulose	410.0
Starch	50.0
Sodium starch glycolate	15.0
Magnesium stearate	5.0
	500.0

(iii) Capsule	mg/capsule
Compound of Formula (I)-(V)	10.0
Colloidal silicon dioxide	1.5
Lactose	465.5
Pregelatinized starch	120.0
Magnesium stearate	3.0
	600.0

(iv) Injection 1 (1 mg/ml)	mg/ml
Compound of Formula (I)-(V)	1.0
Dibasic sodium phosphate	12.0
Monobasic sodium phosphate	0.7
Sodium chloride	4.5
01 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(v) Injection 2 (10 mg/ml)	mg/ml
Compound of Formula (I)-(V)	10.0
Monobasic sodium phosphate	0.3
Dibasic sodium phosphate	1.1
Polyethylene glycol 400	200.0
01 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

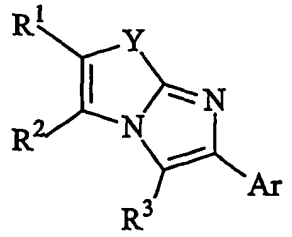
(vi) Aerosol	mg/can
Compound of Formula (I)-(V)	20.0
Oleic acid	10.0
Trichloromonofluoromethane	5,000.0
Dichlorodifluoromethane	10,000.0
Dichlorotetrafluoroethane	5,000.0

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art.

All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

What is claimed is

1. A therapeutic method for suppressing STAT-6 activity and/or for inhibiting the IL-4/IL-13 signal transduction pathways comprising administering to a mammal subject to a pathology amenable to treatment by STAT-6 suppression an effective amount of a compound of formula (I):



(I)

wherein R^1, R^2 and R^3 are independently hydrogen, halo, hydroxy, cyano, $N(R_a)(R_b)$, $S(R_a)$, NO_2, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_7)$alkanoyl, $(C_2\text{-}C_7)$alkanoyloxy, or $(C_3\text{-}C_7)$cycloalkyl or R^1 and R^2 taken together are benzo, optionally substituted by R^1, $(C_3\text{-}C_5)$alkylene or methylene dioxy; wherein R_a and R_b are each independently hydrogen, $(C_1\text{-}C_3)$alkyl, $(C_2\text{-}C_4)$alkanoyl, phenyl, benzyl, or phenethyl; or R_a and R_b together with the nitrogen to which they are attached are a 5-6 membered heterocyclic ring, preferably a pyrrolidino, piperidino or morpholino ring;

Ar is aryl, heteroaryl, or a 5-6 membered heterocyclic ring, preferably comprising 1-3 $N(R_a)$, nonperoxide O or S atoms, such as a pyrrolidino, piperidino or morpholino ring, optionally substituted with 1-5, preferably 1-2, halo, CF_3, hydroxy, CN, $N(R_a)(R_b)$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_7)$alkanoyl, $(C_2\text{-}C_7)$alkanoyloxy, $(C_3\text{-}C_7)$cycloalkyl, $(C_2\text{-}C_6)$alkanoyl, $(C_2\text{-}C_6)$alkenyl, or phenyl;

Y is oxy (–O–), $S(O)_{0\text{-}2}$, Se, $C(R^1)(R^3)$, $N(R_a)$, or –P–;

or a pharmaceutically acceptable salt thereof.

2. The method of claim 1 wherein R^1 and R^2 together is butylene or benzo.

3. The method of claim 1 wherein R^3 is H.

4. The method of claim 1 wherein Ar is phenyl, 4-pyridyl or 2-thienyl.

5. The method of claim 1 wherein Ar is a 5-6 membered heterocyclic ring, comprising 1-3 $N(R_a)$, nonperoxide O or S atoms.

6. The method of claim 1 wherein Ar is pyrrolidino, piperidino or morpholino.

7. The method of claim 1 wherein Y is oxy (–O–), $S(O)_{0-2}$, $C(R^1)(R^3)$, NR^1, or –P–;

8. The method of claim 1 wherein Y is O, $N(R_a)$ or P.

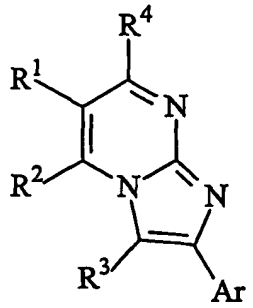
9. The method of claim 1 wherein Y is S.

10. The method of claim 1 wherein $N(R_a)(R_b)$ is amino.

11. The method of claim 1 wherein halo is Br or F.

12. The method of claim 1 wherein $N(R_a)(R_b)$ is pyrrolidino, piperidino or morpholino.

13. A therapeutic method for suppressing STAT-6 activity and/or for inhibiting the IL-4/IL-13 signal transduction pathways comprising administering to a mammal subject to a pathology amenable to treatment by STAT-6 suppression, an effective amount of a compound of formula (II):



(II)

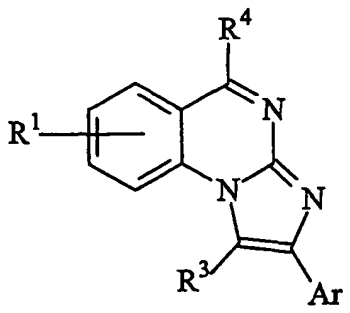
wherein R^1, R^2, $R^3$and $R^4$are independently hydrogen, halo, hydroxy, cyano, $N(R_a)(R_b)$, $S(R_a)$, NO_2, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_2$-$C_6)$alkynyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_7)$alkanoyl, $(C_2$-$C_7)$alkanoyloxy, or $(C_3$-$C_7)$cycloalkyl or R^1 and R^2 taken together are benzo, optionally substituted by R^1, $(C_3$-$C_5)$alkylene or methylene dioxy; wherein R_a and R_b are each independently hydrogen, $(C_1$-$C_3)$alkyl, $(C_2$-$C_4)$alkanoyl, phenyl, benzyl, or phenethyl; or R_a and R_b together with the nitrogen to which they are attached are a 5-6 membered heterocyclic ring, or R^1 and R^4 together with the atoms to which they are attached are benzo, C_3-C_5 alkylidene or methylenedioxy;

Ar is aryl, heteroaryl, or a 5-6 membered heterocyclic ring, preferably comprising 1-3 $N(R_a)$, nonperoxide O or S atoms, such as a pyrrolidino, piperidino or morpholino ring, optionally substituted with 1-5, preferably 1-2, halo, CF_3, hydroxy, CN, $N(R_a)(R_b)$, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_2$-$C_7)$alkanoyl, $(C_2$-$C_7)$alkanoyloxy, $(C_3$-$C_7)$cycloalkyl, $(C_2$-$C_6)$alkanoyl, $(C_2$-$C_6)$alkenyl, or phenyl;

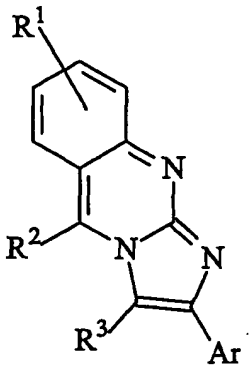
or a pharmaceutically acceptable salt thereof.

14. The method of claim 13 wherein $N(R_a)(R_b)$ is pyrrolidino, piperidino or morpholino.

15. The method of claim 13 wherein the compound of formula (II) has formula (IIa) or (IIb):



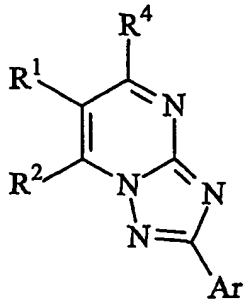
(IIa) and



(IIb)

or a pharmaceutically acceptable salt thereof.

16. A therapeutic method for suppressing STAT-6 activity and/or for inhibiting the IL-4/IL-13 signal transduction pathways comprising administering to a mammal subject to a pathology amenable to treatment by STAT-6 suppression, an effective amount of a compound of formula (III):



(III)

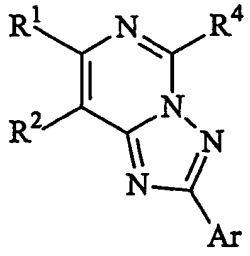
wherein R^1, R^2, and $R^4$are independently hydrogen, halo, hydroxy, cyano, $N(R_a)(R_b)$, $S(R_a)$, NO_2, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_7)$alkanoyl, $(C_2\text{-}C_7)$alkanoyloxy, or $(C_3\text{-}C_7)$cycloalkyl or R^1 and R^2 taken together are benzo, optionally substituted by R^1, $(C_3\text{-}C_5)$alkylene or methylene dioxy; wherein R_a and R_b are each independently hydrogen, $(C_1\text{-}C_3)$alkyl, $(C_2\text{-}C_4)$alkanoyl, phenyl, benzyl, or phenethyl; or R_a and R_b together with the nitrogen to which

they are attached are a 5-6 membered heterocyclic ring, or R^1 and R^4 together with the atoms to which they are attached are benzo, C_3-C_5 alkylidene or methylenedioxy;

Ar is aryl, heteroaryl, or a 5-6 membered heterocyclic ring, preferably comprising 1-3 $N(R_a)$, nonperoxide O or S atoms, such as a pyrrolidino, piperidino or morpholino ring, optionally substituted with 1-5, preferably 1-2, halo, CF_3, hydroxy, CN, $N(R_a)(R_b)$, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_2$-$C_7)$alkanoyl, $(C_2$-$C_7)$alkanoyloxy, $(C_3$-$C_7)$cycloalkyl, $(C_2$-$C_6)$alkanoyl, $(C_2$-$C_6)$alkenyl, or phenyl.

or a pharmaceutically acceptable salt thereof.

17. A therapeutic method for suppressing STAT-6 activity and/or for inhibiting the IL-4/IL-13 signal transduction pathways comprising administering to a mammal subject to a pathology amenable to treatment by STAT-6 suppression, an effective amount of a compound of formula (IV):

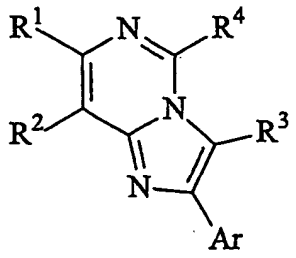


(IV)

wherein R^1, R^2 and $R^4$are independently hydrogen, halo, hydroxy, cyano, $N(R_a)(R_b)$, $S(R_a)$, NO_2, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_2$-$C_6)$alkynyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_7)$alkanoyl, $(C_2$-$C_7)$alkanoyloxy, or $(C_3$-$C_7)$cycloalkyl or R^1 and R^2 taken together are benzo, optionally substituted by R^1, $(C_3$-$C_5)$alkylene or methylene dioxy; wherein R_a and R_b are each independently hydrogen, $(C_1$-$C_3)$alkyl, $(C_2$-$C_4)$alkanoyl, phenyl, benzyl, or phenethyl; or R_a and R_b together with the nitrogen to which they are attached are a 5-6 membered heterocyclic ring;

Ar is aryl, heteroaryl, or a 5-6 membered heterocyclic ring, preferably comprising 1-3 $N(R_a)$, nonperoxide O or S atoms, such as a pyrrolidino, piperidino or morpholino ring, optionally substituted with 1-5, preferably 1-2, halo, CF_3, hydroxy, CN, $N(R_a)(R_b)$, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_2-C_7)alkanoyl, (C_2-C_7)alkanoyloxy, (C_3-C_7)cycloalkyl, (C_2-C_6)alkanoyl, (C_2-C_6)alkenyl, or phenyl.
or a pharmaceutically acceptable salt thereof.

18. A therapeutic method for suppressing STAT-6 activity and/or for inhibiting the IL-4/IL-13 signal transduction pathways comprising administering to a mammal subject to a pathology amenable to treatment by STAT-6 suppression, an effective amount of a compound of formula (V):



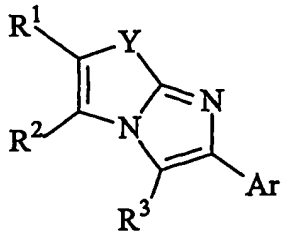
(V)

wherein R^1, R^2, $R^3$and $R^4$are independently hydrogen, halo, hydroxy, cyano, $N(R_a)(R_b)$, $S(R_a)$, NO_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_2-C_7)alkanoyl, (C_2-C_7)alkanoyloxy, or (C_3-C_7)cycloalkyl or R^1 and R^2 taken together are benzo, optionally substituted by R^1, (C_3-C_5)alkylene or methylene dioxy; wherein R_a and R_b are each independently hydrogen, (C_1-C_3)alkyl, (C_2-C_4)alkanoyl, phenyl, benzyl, or phenethyl; or R_a and R_b together with the nitrogen to which they are attached are a 5-6 membered heterocyclic ring;
Ar is aryl, heteroaryl, or a 5-6 membered heterocyclic ring, preferably comprising 1-3 $N(R_a)$, nonperoxide O or S atoms, such as a pyrrolidino,

piperidino or morpholino ring, optionally substituted with 1-5, preferably 1-2, halo, CF_3, hydroxy, CN, $N(R_a)(R_b)$, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_2-C_7)alkanoyl, (C_2-C_7)alkanoyloxy, (C_3-C_7)cycloalkyl, (C_2-C_6)alkanoyl, (C_2-C_6)alkenyl, or phenyl.

or a pharmaceutically acceptable salt thereof.

19. A compound of formula (I):



(I)

wherein R^1, R^2 and R^3 are independently hydrogen, halo, hydroxy, cyano, $N(R_a)(R_b)$, $S(R_a)$, NO_2, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_2-C_6)alkynyl, (C_2-C_6)alkenyl, (C_2-C_7)alkanoyl, (C_2-C_7)alkanoyloxy, or (C_3-C_7)cycloalkyl or R^1 and R^2 taken together are benzo, optionally substituted by R^1, (C_3-C_5)alkylene or methylene dioxy; wherein R_a and R_b are each independently hydrogen, (C_1-C_3)alkyl, (C_2-C_4)alkanoyl, phenyl, benzyl, or phenethyl; or R_a and R_b together with the nitrogen to which they are attached are a 5-6 membered heterocyclic ring, preferably a pyrrolidino, piperidino or morpholino ring;

Ar is aryl or heteroaryl, optionally substituted with 1-5 CF_3, hydroxy, CN, $N(R_a)(R_b)$, (C_1-C_6)alkyl, (C_2-C_7)alkanoyl, (C_2-C_7)alkanoyloxy, (C_3-C_7)cycloalkyl, (C_2-C_6)alkanoyl, (C_2-C_6)alkenyl, or phenyl.

Y is oxy (–O–), $S(O)_{0-2}$, Se, $C(R^1)(R^3)$, $N(R_a)$, or –P–;

or a pharmaceutically acceptable salt thereof;

provided that R^1 and R^2 are not benzo or (C_3-C_5)alkylidenyl when Ar is aryl; and

provided that when Y is S, Ar is not phenyl.

20. The compound of claim 19 wherein R^1 or R^2 are independently hydroxy, cyano, -$N(R_a)(R_b)$, $S(R_a)$, NO_2, $(C_2$-$C_7)$alkanoyl, or $(C_2$-$C_7)$alkanoyloxy; Ar is heteroaryl or phenyl substituted with cyano, $(C_2$-$C_7)$alkanoyl, $(C_2$-$C_7)$alkanolyoxy, $(C_2$-$C_7)$cycloalkyl or $(C_2$-$C_6)$alkenyl; and Y is Se, SO, SO_2, $C(R_1)(R_3)$ or P.

21. The compound of claim 19 wherein R^1 and R^2 together is butylene or benzo.

22. The compound of claim 19 wherein R^3 is H.

23. The compound of claim 19 wherein Y is oxy (–O–), $S(O)_{0-2}$, $C(R^1)(R^3)$, NR^1, or –P–;

24. The compound of claim 19 wherein Y is O, $N(R_a)$ or P.

25. The compound of claim 19 wherein Ar is phenyl, 4-pyridyl or 2-thienyl.

26. The compound of claim 19 wherein Ar is heteroaryl or phenyl substituted with CN, $(C_2$-$C_7)$alkanoyl, $(C_2$-$C_7)$alkanolyoxy, $(C_2$-$C_7)$cycloalkyl or $(C_2$-$C_6)$alkenyl.

27. The compound of claim 19 wherein Ar is a 5-6 membered heterocyclic ring, comprising 1-3 $N(R_a)$, nonperoxide O or S atoms.

28. The compound of claim 19 wherein Ar is pyrrolidino, piperidino or morpholino.

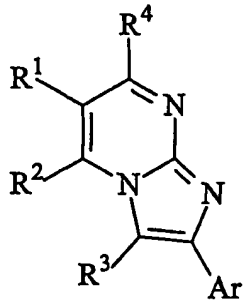
29. The compound of claim 19 wherein Y is S.

30. The compound of claim 19 wherein $N(R_a)(R_b)$ is amino.

31. The method of claim 19 wherein halo is Br or F.

32. The compound of claim 19 wherein $N(R_a)(R_b)$ is pyrrolidino, piperidino or morpholino.

33. A compound of formula (II):



(II)

wherein R^1, R^2, $R^3$and $R^4$are independently hydrogen, halo, hydroxy, cyano, $N(R_a)(R_b)$, $S(R_a)$, NO_2, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, $(C_2$-$C_6)$alkynyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_7)$alkanoyl, $(C_2$-$C_7)$alkanoyloxy, or $(C_3$-$C_7)$cycloalkyl or R^1 and R^2 taken together are benzo, optionally substituted by R^1, $(C_3$-$C_5)$alkylene or methylene dioxy; wherein R_a and R_b are each independently hydrogen, $(C_1$-$C_3)$alkyl, $(C_2$-$C_4)$alkanoyl, phenyl, benzyl, or phenethyl; or R_a and R_b together with the nitrogen to which they are attached are a 5-6 membered heterocyclic ring, or R^1 and R^4 together with the atoms to which they are attached are benzo, C_3-C_5 alkylidene or methylenedioxy;

Ar is aryl, heteroaryl, or a 5-6 membered heterocyclic ring, preferably comprising 1-3 $N(R_a)$, nonperoxide O or S atoms, such as a pyrrolidino, piperidino or morpholino ring, optionally substituted with 1-5, preferably 1-2, halo, CF_3, hydroxy, CN, $N(R_a)(R_b)$, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy,

(C_2-C_7)alkanoyl, (C_2-C_7)alkanoyloxy, (C_3-C_7)cycloalkyl, (C_2-C_6)alkanoyl, (C_2-C_6)alkenyl, or phenyl;

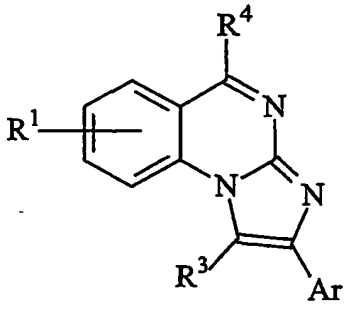
or a pharmaceutically acceptable salt thereof;

provided that R^1 and R^2 are not benzo when Ar is phenyl; and

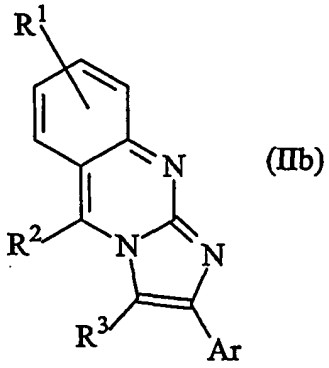
provided that R^4 is not OH when R^1 and R^2 is benzo.

34. The compound of claim 33 wherein one of R^1, R^2, R^3 and R^4 is $N(R_a)(R_b)$ and with the nitrogen to which they are attached is pyrrolidino, piperidino or morpholino.

35. The compound of claim 33 having formula (IIa) and (IIb):



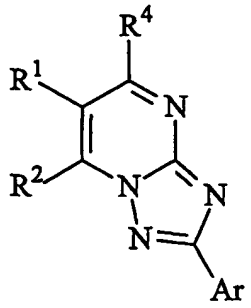
(IIa) and



(IIb)

or a pharmaceutically acceptable salt thereof.

36. A compound having formula (III):



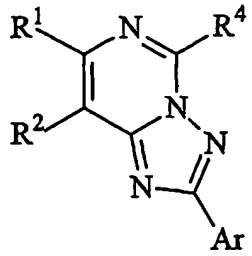
(III)

wherein R^1, R^2, and $R^4$are independently hydrogen, halo, hydroxy, cyano, $N(R_a)(R_b)$, $S(R_a)$, NO_2, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_7)$alkanoyl, $(C_2\text{-}C_7)$alkanoyloxy, or $(C_3\text{-}C_7)$cycloalkyl or R^1 and R^2 taken together are benzo, optionally substituted by R^1, $(C_3\text{-}C_5)$alkylene or methylene dioxy; wherein R_a and R_b are each independently hydrogen, $(C_1\text{-}C_3)$alkyl, $(C_2\text{-}C_4)$alkanoyl, phenyl, benzyl, or phenethyl; or R_a and R_b together with the nitrogen to which they are attached are a 5-6 membered heterocyclic ring, or R^1 and R^4 together with the atoms to which they are attached are benzo, $C_3\text{-}C_5$ alkylidene or methylenedioxy;

Ar is aryl, heteroaryl, or a 5-6 membered heterocyclic ring, preferably comprising 1-3 $N(R_a)$, nonperoxide O or S atoms, such as a pyrrolidino, piperidino or morpholino ring, optionally substituted with 1-5, preferably 1-2, halo, CF_3, hydroxy, CN, $N(R_a)(R_b)$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_7)$alkanoyl, $(C_2\text{-}C_7)$alkanoyloxy, $(C_3\text{-}C_7)$cycloalkyl, $(C_2\text{-}C_6)$alkanoyl, $(C_2\text{-}C_6)$alkenyl, or phenyl.

or a pharmaceutically acceptable salt thereof.

37. A compound having formula (IV):



(IV)

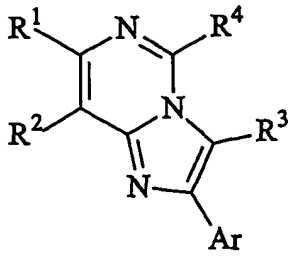
wherein R^1, R^2 and $R^4$are independently hydrogen, halo, hydroxy, cyano, $N(R_a)(R_b)$, $S(R_a)$, NO_2, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_7)$alkanoyl, $(C_2\text{-}C_7)$alkanoyloxy, or $(C_3\text{-}C_7)$cycloalkyl or R^1 and R^2 taken together are benzo, optionally substituted by R^1, $(C_3\text{-}C_5)$alkylene or methylene dioxy; wherein R_a and R_b are each independently hydrogen, $(C_1\text{-}C_3)$alkyl, $(C_2\text{-}C_4)$alkanoyl, phenyl, benzyl, or phenethyl; or R_a and R_b together with the nitrogen to which they are attached are a 5-6 membered heterocyclic ring;

Ar is aryl, heteroaryl, or a 5-6 membered heterocyclic ring, preferably comprising 1-3 $N(R_a)$, nonperoxide O or S atoms, such as a pyrrolidino, piperidino or morpholino ring, optionally substituted with 1-5, preferably 1-2, halo, CF_3, hydroxy, CN, $N(R_a)(R_b)$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_7)$alkanoyl, $(C_2\text{-}C_7)$alkanoyloxy, $(C_3\text{-}C_7)$cycloalkyl, $(C_2\text{-}C_6)$alkanoyl, $(C_2\text{-}C_6)$alkenyl, or phenyl.

or a pharmaceutically acceptable salt thereof; and

provided that R^1 and R^2 are not benzo when R^4 is H or OH.

38. A compound having formula (V):



(V)

wherein R^1, R^2, $R^3$and $R^4$are independently hydrogen, halo, hydroxy, cyano, $N(R_a)(R_b)$, $S(R_a)$, NO_2, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$alkynyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_7)$alkanoyl, $(C_2\text{-}C_7)$alkanoyloxy, or $(C_3\text{-}C_7)$cycloalkyl or R^1 and R^2 taken together are benzo, optionally substituted by R^1, $(C_3\text{-}C_5)$alkylene or methylene dioxy; wherein R_a and R_b are each independently hydrogen, $(C_1\text{-}C_3)$alkyl, $(C_2\text{-}C_4)$alkanoyl, phenyl, benzyl, or phenethyl; or R_a and R_b together with the nitrogen to which they are attached are a 5-6 membered heterocyclic ring, or R^1 and R^4 together with the atoms to which they are attached are benzo, $C_3\text{-}C_5$ alkylidene or methylenedioxy;

Ar is aryl, heteroaryl, or a 5-6 membered heterocyclic ring, preferably comprising 1-3 $N(R_a)$, nonperoxide O or S atoms, such as a pyrrolidino, piperidino or morpholino ring, optionally substituted with 1-5, preferably 1-2, halo, CF_3, hydroxy, CN, $N(R_a)(R_b)$, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_7)$alkanoyl, $(C_2\text{-}C_7)$alkanoyloxy, $(C_3\text{-}C_7)$cycloalkyl, $(C_2\text{-}C_6)$alkanoyl, $(C_2\text{-}C_6)$alkenyl, or phenyl.

or a pharmaceutically acceptable salt thereof; and

provided that Ar is not 4-methoxyphenyl when R^1 and R^2 are benzo and R^4 is H.

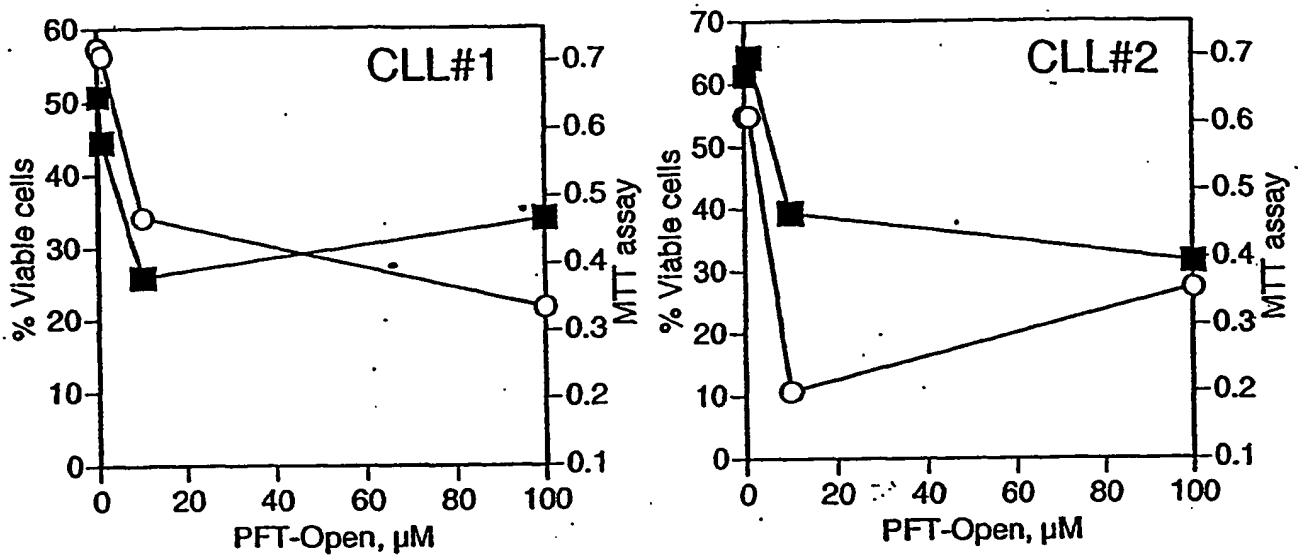
39. The compound as described in any of claims 19, 33, 36, 37 and 38 for use in medical therapy.

40. The use of a compound as described in any of claims 19, 33, 36, 37 and 38 for the manufacture of a medicament useful for the treatment of a disease in a mammal, such as a human.

FIGURE 1

Effect of the p53-Inhibitory compound on B-CLL viability

Open ring: cytotoxic



Closed ring: not cytotoxic

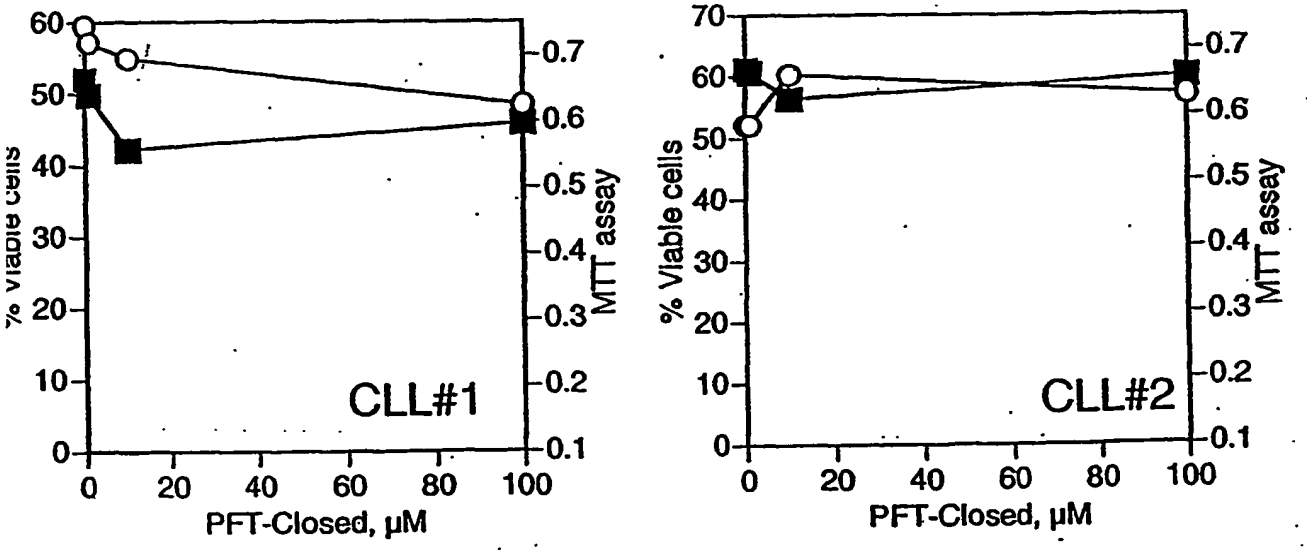
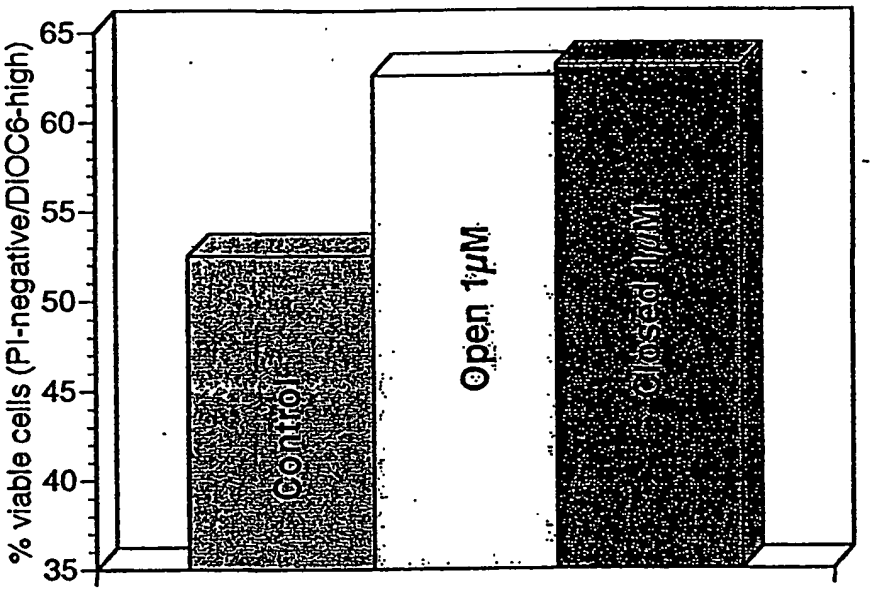


FIGURE 2

CLL#1: protection against spontaneous apoptosis



CLL#2: protection against fludarabine-induced apoptosis

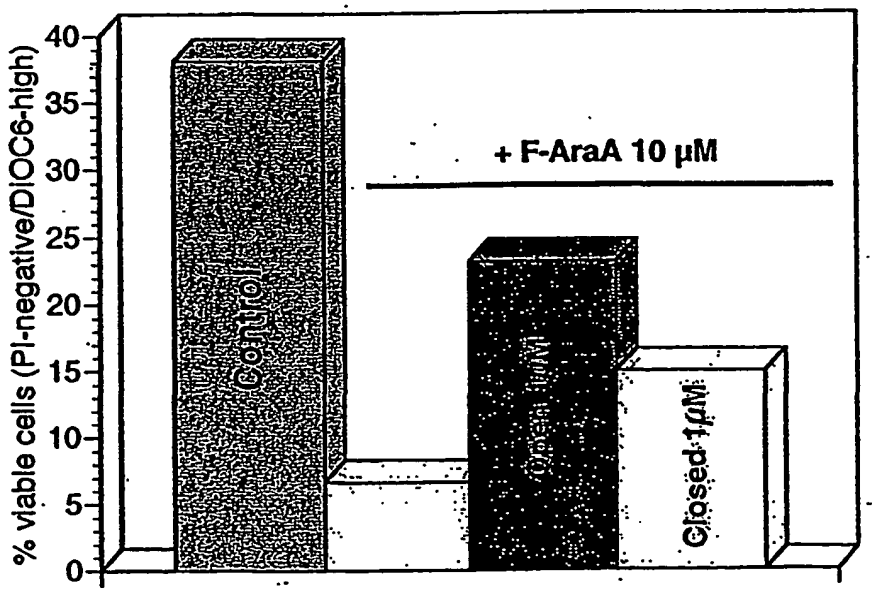


Figure 3

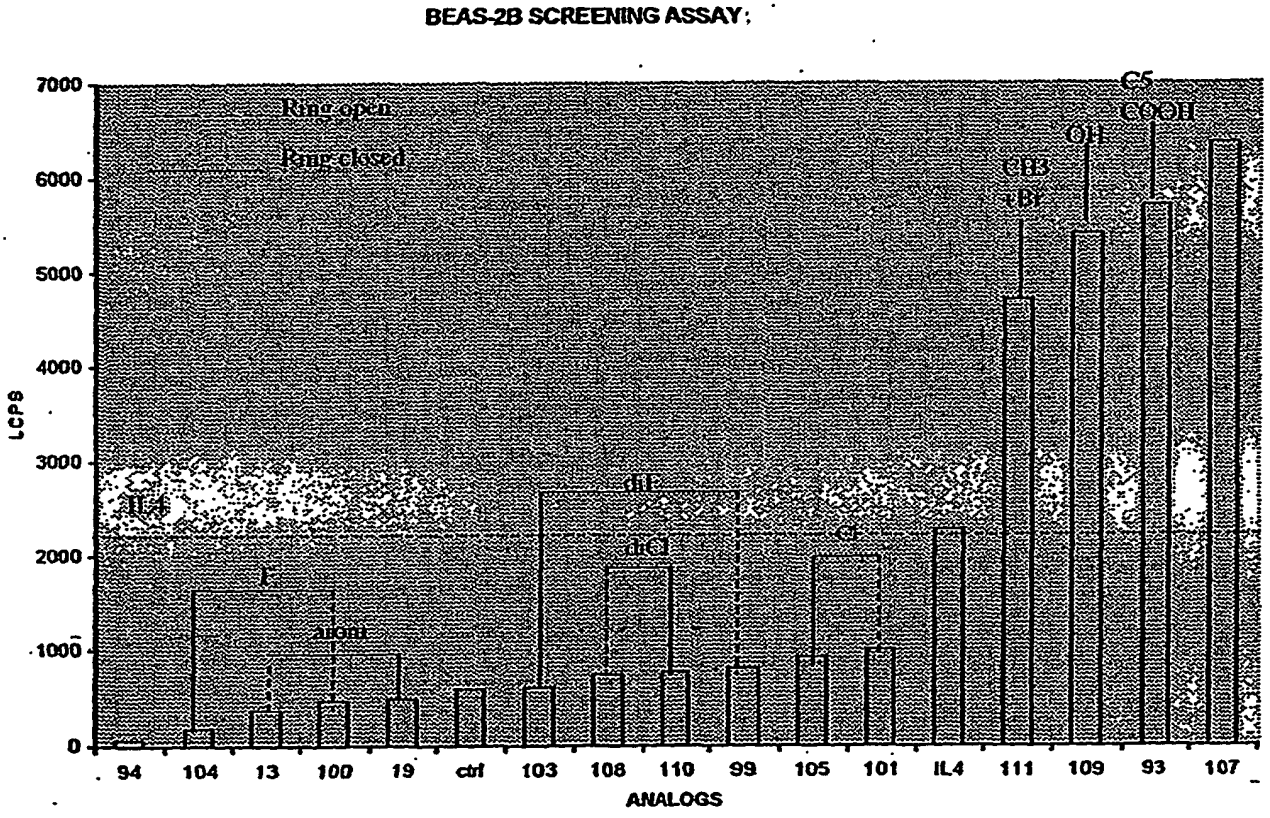
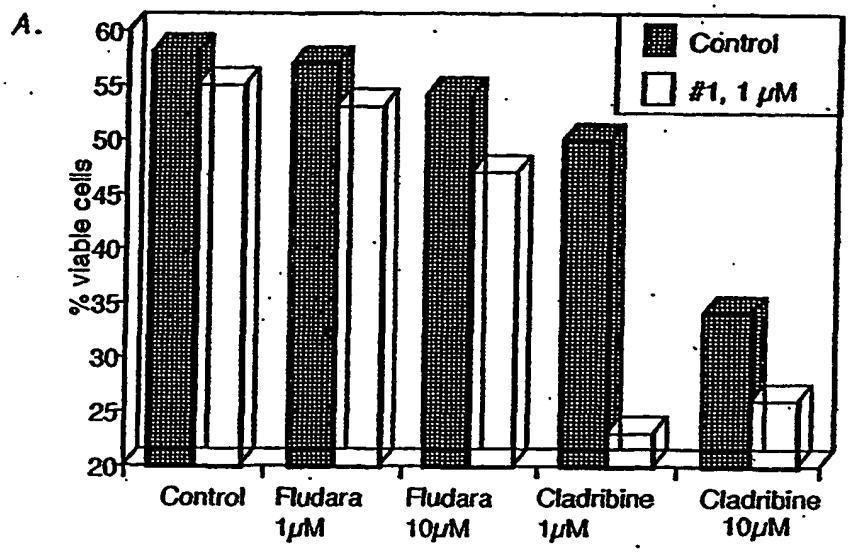

BEAS-2B SCREENING ASSAY:
LCPS
7000
6000
5000
4000
3000
2000
1000
0
Ring open
Ring closed
IL4
F
atom
diF
diCl
Cl
CH3
Br
OH
COOH
94
104
13
100
19
ctrl
103
108
110
99
105
101
IL4
111
109
93
107
ANALOGS

Figure 4


A.
% viable cells
60
55
50
45
40
35
30
25
20
Control
#1, 1 μM
Control
Fludara 1μM
Fludara 10μM
Cladribine 1μM
Cladribine 10μM

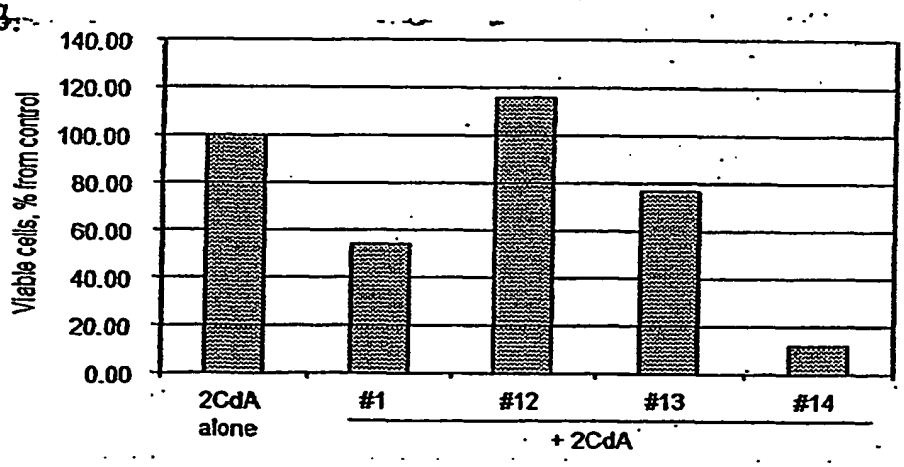
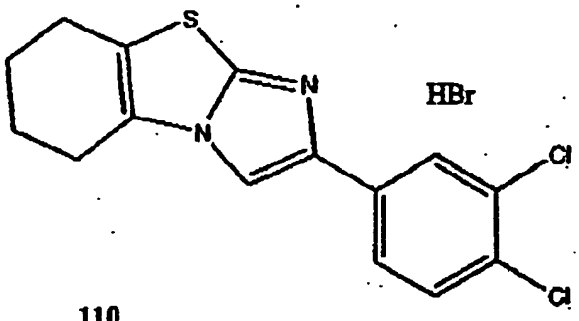
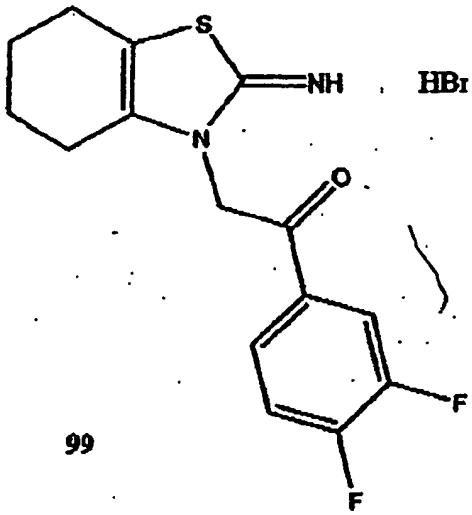

B.
Viable cells, % from control
140.00
120.00
100.00
80.00
60.00
40.00
20.00
0.00
2CdA alone
#1
#12
#13
#14
+ 2CdA

Figure 5.



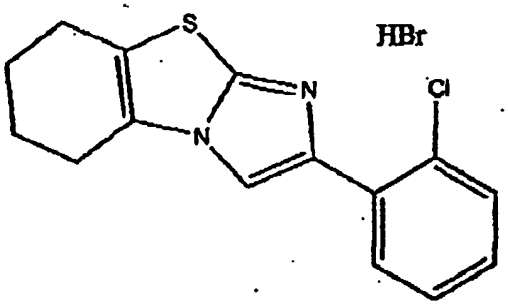
110

$C_{15}H_{13}BrCl_2N_2S$
Mol. Wt.: 404.15



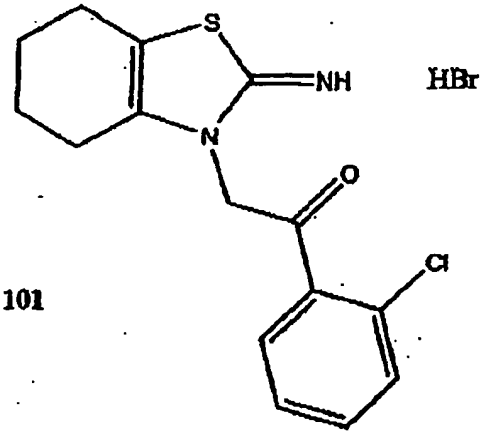
99

$C_{15}H_{15}BrF_2N_2OS$
Mol. Wt.: 389.26



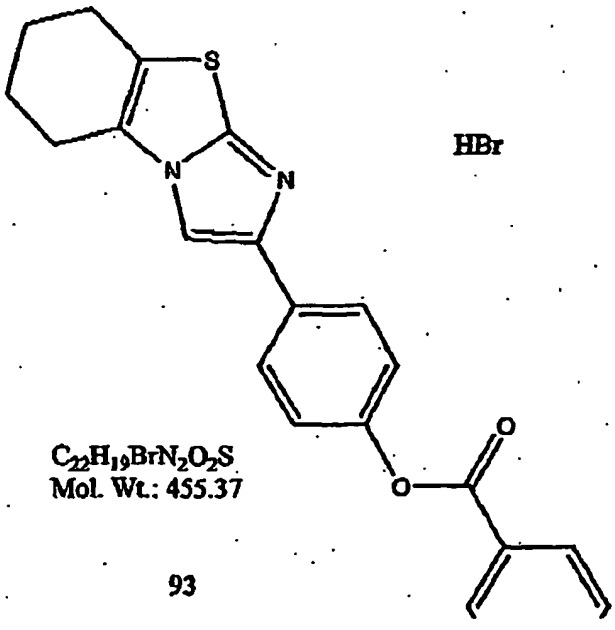
105

$C_{15}H_{14}BrClN_2S$
Mol. Wt.: 369.71



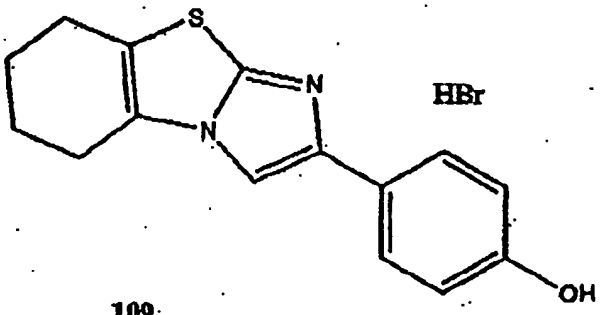
101

$C_{15}H_{16}BrClN_2OS$
Mol. Wt.: 387.72



$C_{22}H_{19}BrN_2O_2S$
Mol. Wt.: 455.37

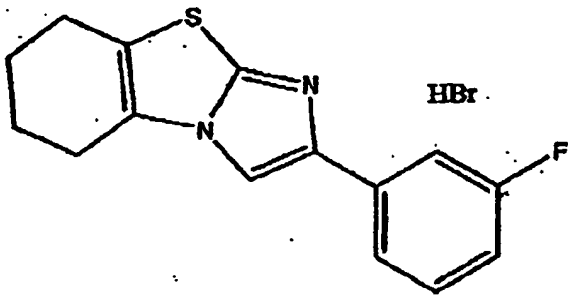
93



109

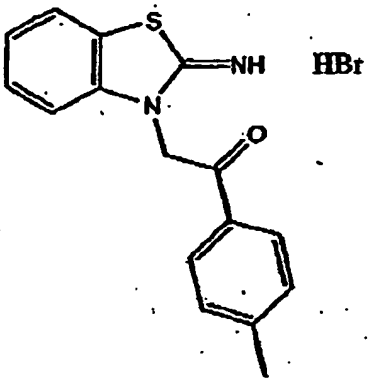
$C_{15}H_{15}BrN_2OS$

Figure 5 (cont)



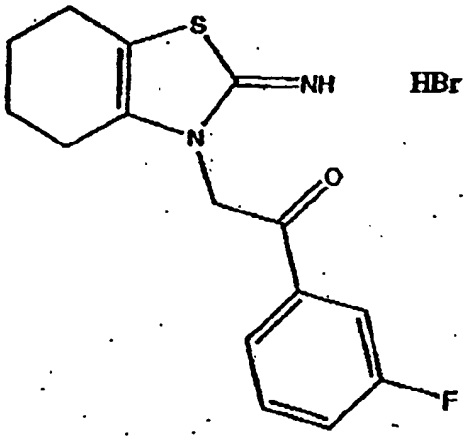
$C_{15}H_{14}BrFN_2S$
Mol. Wt.: 353.25

104



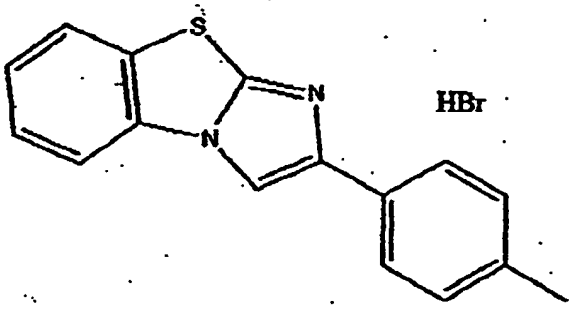
$C_{16}H_{15}BrN_2OS$
Mol. Wt.: 363.27

13



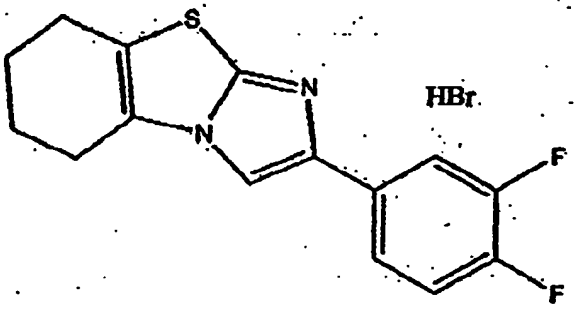
$C_{15}H_{16}BrFN_2OS$
Mol. Wt.: 371.27

100



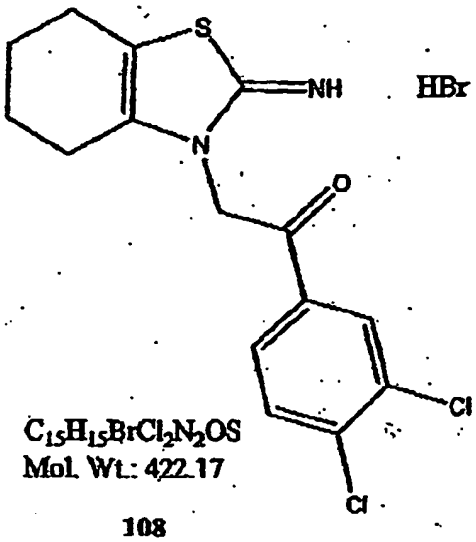
$C_{16}H_{13}BrN_2S$
Mol. Wt.: 345.26

19



$C_{15}H_{13}BrF_2N_2S$
Mol. Wt.: 371.24

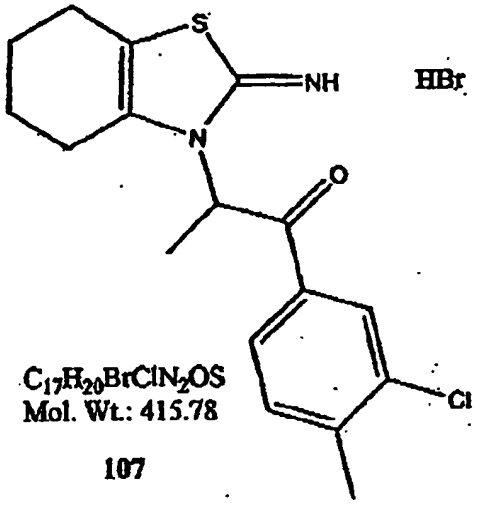
103



$C_{15}H_{15}BrCl_2N_2OS$
Mol. Wt.: 422.17

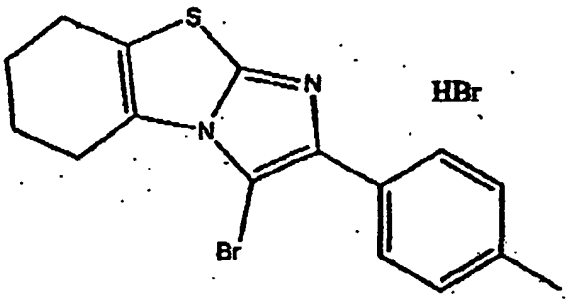
108

Figure 5 (cont)



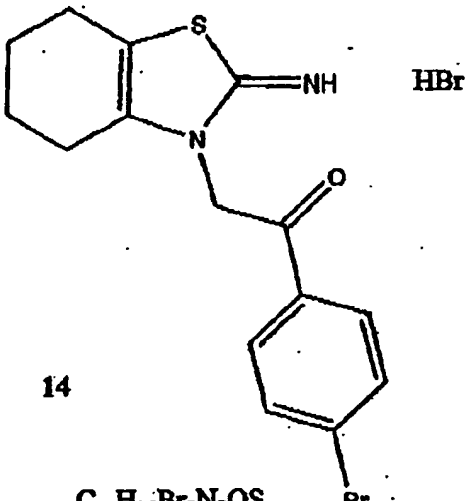
$C_{17}H_{20}BrClN_2OS$
Mol. Wt.: 415.78

107



111 and 12

$C_{16}H_{16}Br_2N_2S$
Mol. Wt.: 428.19



14

$C_{15}H_{16}Br_2N_2OS$
Mol. Wt.: 432.17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/25175

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 487/04, 513/04; A61K 31/425, 31/505
US CL : 514/258,267,368; 544/250, 251, 263, 281; 548/154
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
US CL : 514/258, 267, 368; 544/250, 251, 263, 281; 548/154

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE- Structure search in file registry and crossover into Caplus file.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5,696,260 (SHAW ET AL) 09 December 1997, see entire document	18-38
X	JP 11-106340 INOUE ET AL) 20 April 1999 (20-04-99) see entire document	1-12
X	WO 00/44364 (GUDKOV ET AL) 03 August 2000 (03-08-00) see entire document	1-12
X	Database REGISTRY FILE on STN (Columbus,OH USA), No.115:71526, "Guanidine-annelated heterocycles XIII", abstract Hu et al, February 1991.	36
X	Database REGISTRY FILE on STN (Columbus , OH USA), NO.13422676, Synthesis and antiinflammatory evaluation of new 2- and 3-substituted 1,2,4-triazolo[4,3-c] and [1,5-c]quinazoline derivatives", abstract Hu et al, February 1991	37

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2001 (20.11.2001)	31 DEC 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Bernard Dentz Telephone No. 703 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/25175

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: 1-18 and 33-38 in full and 39 and 40 in part

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/25175

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

I. Claims 1-12 drawn to a therapeutic method using cpds. where an imidazo ring is fused to a 5-membered ring.
II. Claims 13-15 and 33-35 drawn to 1,2-a imidazopyrimidines and their use in a therapeutic method.
III. Claims 16 and 36 drawn to triazolopyrimidines where the triazolo moiety is fused to the a-bond of the pyrimidine and their use in a therapeutic method.
IV. claims 17 and 37 drawn to triazolopyrimidnes where the triazolo moiety is fused to the c-bond of the pyrimidine moiety and theier use in a therapeutic method.
V. Claims 18 and 38 drawn to 1,2-c imidazopyrimidines and their use in a therapeutic method.
VI. Claims 19-32 drawn to cpds. Where an imidazo ring is fused to a 5-membred ring.

[0007] Another RTK subfamily consists of insulin receptor (IR), insulin-like growth factor I receptor (IGF-1R) and insulin receptor related receptor (IRR). IR and IGF-1R interact with insulin, IGF-I and IGF-II to form a heterotetramer of two entirely extracellular glycosylated subunits and two subunits which cross the cell membrane and which contain the tyrosine kinase domain.

[0008] A third RTK subfamily is referred to as the platelet derived growth factor receptor ("PDGFR") group, which includes PDGFR, PDGFR, CSFIR, c-kit and c-fms. These receptors consist of glycosylated extracellular domains composed of variable numbers of immunoglobin-like loops and an intracellular domain wherein the tyrosine kinase domain is interrupted by unrelated amino acid sequences.

[0009] Another group which, because of its similarity to the PDGFR subfamily, is sometimes subsumed into the later group is the fetus liver kinase ("flk") receptor subfamily. This group is believed to be made of up of kinase insert domain-receptor fetal liver kinase-1 (KDR/FLK-1), flk-1R, flk-4 and fms-like tyrosine kinase 1 (flt-1). Still another member of the growth factor receptor family is the vascular endothelial growth factor ("VEGF") receptor subgroup. VEGF is a dimeric glycoprotein similar to PDGF but has different biological functions and target cell specificity *in vivo*. In particular, VEGF is presently thought to play an essential role is vasculogenesis and angiogenesis.

[0010] A further member of the tyrosine kinase growth factor receptor family is the fibroblast growth factor ("FGF") receptor subgroup. This group consists of four receptors, FGFR1-4, and seven ligands, FGF1-7. While not yet well defined, it appears that the receptors consist of a glycosylated extracellular domain containing a variable number of immunoglobin-like loops and an intracellular domain in which the tyrosine kinase sequence is interrupted by regions of unrelated amino acid sequences.

[0011] Still another member of the tyrosine kinase growth factor receptor family is MET, often referred to as c-Met. c-met is also known as hepatocyte growth factor receptor or scatter factor receptor. c-Met is thought to play a role in primary tumor growth and metastasis.

[0012] A more complete listing of the known RTK subfamilies is described in Plowman *et al.*, DN&P, 7(6):334-339 (1994), which is incorporated by reference, including any drawings, as if fully set forth herein.

[0013] In addition to the RTKs, there also exists a family of entirely intracellular PTKs called "non-receptor tyrosine kinases" or "cellular tyrosine kinases." This latter designation, abbreviated "CTK," will be used herein. CTKs do not contain extracellular and transmembrane domains. At present, over 24 CTKs in 11 subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes, Fps, Fak, Jak and Ack) have been identified. The Src subfamily appear so far to be the largest group of CTKs and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk.

For a more detailed discussion of CTKs, see Bolen, *Oncogene*, 8:2025-2031 (1993), which is incorporated by reference, including any drawings, as if fully set forth herein.

[0014] The serine/threonine kinases, STKs, like the CTKs, are predominantly intracellular although there are a few receptor kinases of the STK type. STKs are the most common of the cytosolic kinases; *i.e.*, kinases that perform their function in that part of the cytoplasm other than the cytoplasmic organelles and cytoskelton. The cytosol is the region within the cell where much of the cell's intermediary metabolic and biosynthetic activity occurs; *e.g.*, it is in the cytosol that proteins are synthesized on ribosomes.

[0015] RTKs, CTKs and STKs have all been implicated in a host of pathogenic conditions including, significantly, cancer. Other pathogenic conditions which have been associated with PTKs include, without limitation, psoriasis, hepatic cirrhosis, diabetes, angiogenesis, restenosis, ocular diseases, rheumatoid arthritis and other inflammatory disorders, immunological disorders such as autoimmune disease, cardiovascular disease such as atherosclerosis and a variety of renal disorders.

[0016] With regard to cancer, two of the major hypotheses advanced to explain the excessive cellular proliferation that drives tumor development relate to functions known to be PK regulated. That is, it has been suggested that malignant cell growth results from a breakdown in the mechanisms that control cell division and/or differentiation. It has been shown that the protein products of a number of proto-oncogenes are involved in the signal transduction pathways that regulate cell growth and differentiation. These protein products of proto-oncogenes include the extracellular growth factors, transmembrane growth factor PTK receptors (RTKs), cytoplasmic PTKs (CTKs) and cytosolic STKs, discussed above.

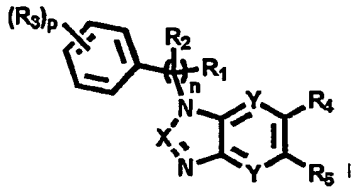
[0017] In view of the apparent link between PK-related cellular activities and wide variety of human disorders, it is no surprise that a great deal of effort is being expended in an attempt to identify ways to modulate PK activity. Some of these have involved biomimetic approaches using large molecules patterned on those involved in the actual cellular processes (*e.g.*, mutant ligands (U.S. Application Serial No. 4,966,849); soluble receptors and antibodies (Application No. WO 94/10202, Kendall and Thomas, *Proc. Nat'l Acad. Sci.*, 90:10705-10709 (1994), Kim, *et al.*, *Nature*, 362:841-844 (1993)); RNA ligands (Jelinek, *et al.*, *Biochemistry*, 33:10450-56); Takano, *et al.*, *Mol. Bio. Cell*, 4:358A (1993); Kinsella, *et al.*, *Exp. Cell Res.*, 199 :56-62 (1992); Wright, *et al.*, *J. Cellular Phys.*, 152:448-57) and tyrosine kinase inhibitors (WO 94/03427; WO 92/21660; WO 91/15495; WO 94/14808; U.S. Patent No. 5,330,992; Mariani, *et al.*, *Proc. Am. Assoc. Cancer Res.*, 35:2268 (1994)).

[0018] In addition to the above, attempts have been made to identify small molecules which act as PK inhibitors. For example, bis-monocylic, bicyclic and heterocyclic aryl compounds (PCT WO 92/20642), vinylene-azaindole derivatives (PCT WO 94/14808) and 1-cyclopropyl-4-pyridylquinolones (U.S. Patent No. 5,330,992) have been described as tyrosine kinase inhibitors. Styryl compounds (U.S. Patent No. 5,217,999), styryl-substituted pyridyl

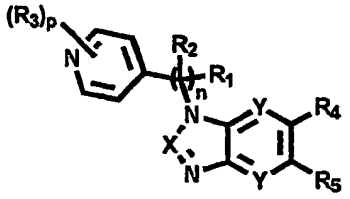
compounds (U.S. Patent No. 5,302,606), quinazoline derivatives (EP Application No. 0 566 266 A1), selenaindoles and selenides (PCT WO 94/03427), tricyclic polyhydroxylic compounds (PCT WO 92/21660) and benzylphosphonic acid compounds (PCT WO 91/15495) have all been described as PTK inhibitors useful in the treatment of cancer.

SUMMARY OF THE INVENTION

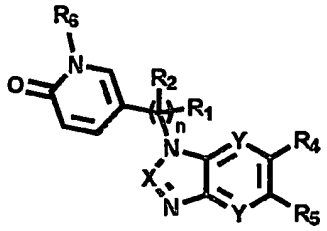
[0019] In one aspect, the invention relates to a compound of the formula I, II or III:



(I)



(II)



(III)

wherein:

X is CH or N;

each Y is independently CH or N;

R_1 and R_2 are independently selected from the group consisting of hydrogen, halogen, -CN, $-COR_7$, $-COOR_7$, $-CONR_7R_8$, $-CF_3$, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl and alkynyl;

R_3 is a substituent selected from the group consisting of F, Cl, -OH, $-OR_7$, $-COR_9$, $-NR_7R_8$, -CN, $-SO_2R_7$, $-S(O)R_7$, $SO_2NR_7R_8$, $-CF_3$, and lower alkyl;

wherein if p is greater than 1, then each R_3 is independently F, Cl, -OH, $-OR_7$, $-COR_9$, $-NR_7R_8$, -CN, $-SO_2R_7$, $-S(O)R_7$, $SO_2NR_7R_8$, $-CF_3$, or lower alkyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, halogen, -OH, $-COR_7$, $-COOR_7$, $-CONR_7R_8$, $-NR_7R_8$, -CN, $-NO_2$, $-S(O)_2R_7$, $-S(O)R_7$, $-SO_2NR_6R_7$, $-CF_3$, $-NR_6C(O)NR_7R_8$, $-NR_6C(O)R_7$, $-NR_6SO_2R_7$ substituted or unsubstituted

cycloalkyl, substituted or unsubstituted heteroalicyclic, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl;

R_6, R_7 and R_8 are independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl, alkynyl, aryl, heteroaryl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl and heteroaryl; or

R_7 and R_8 or R_6 and R_7, together with the atom to which they are attached, form a heteroalicyclic ring optionally substituted with a group selected from the group consisting of alkyl, -OH, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkylamino, dialkylamino;

R_9 is a substituent selected from the group consisting of H, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl, alkynyl, aryl, heteroaryl, dialkylaminoalkyl, heteroaryl and alkylaminoalkyl;

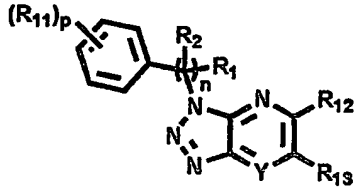
n is 1, 2 or 3, it being understood that when n is greater than 1, the R_1 and R_2 groups on each carbon atom may be the same as or different from the R_1 and R_2 groups on any adjacent carbon atom; and

p is 0, 1, 2 or 3; or

a pharmaceutically acceptable salt thereof.

[0020] In preferred embodiments, the invention relates to compounds of the formulae (I), (II) or (III), wherein (a) n is 1; (b) X is CH; (c) Y is N; and (d) wherein R_3 is F, Cl or $-OR_7$.

[0021] In a second aspect, the invention relates to a compound of the formula IV:



wherein:

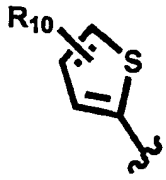
p is 0, 1, 2 or 3;

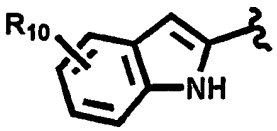
Y is CH or N;

R_1 and R_2 are independently selected from the group consisting of hydrogen, halogen, -CN, $-COR_7$, $-COOR_7$, $-CONR_7R_8$, $-CF_3$, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl and alkynyl;

each R_{11} is independently selected from the group consisting of halogen, -OH, $-OR_7$, $-COR_7$, $-COOR_7$, $-CONR_7R_8$, $-NR_7R_8$, -CN, $-NO_2$, $-S(O)_2R_7$, $-S(O)R_7$, $SO_2NR_7R_8$, $-CF_3$, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl, alkynyl and aryl;

R_{12} is selected from the group consisting of:

,


, and


,

wherein R_{10} is selected from the group consisting of hydrogen, -OH, halogen, $-O(CH_2)_mNR_7R_8$, $-NHC(O)NH(CH_2)_mNR_7R_8$, $-C(O)NR_7R_8$, $-(CH_2)_m$aryl, $-NR_6C(O)R_7$, $-NR_6SO_2R_7$, $-S(CH_2)_mNR_7R_8$, $-SO_2R_7$, -S(O)R_7, and $-SO_2NR_7R_8$;

wherein m is 0, 1, 2 or 3;

R_{13} is selected from the group consisting of hydrogen, halogen, $-OR_7$, $-COR_7$, $-COOR_7$, $-CONR_7R_8$, $-NR_7R_8$, -CN, $-NO_2$, $-S(O)_2R_7$, -S(O)R_7, $-SO_2NR_6R_7$, $-CF_3$, lower alkyl, cycloalkyl, heteroalicyclic, heteroaryl, alkenyl, alkynyl, and aryl;

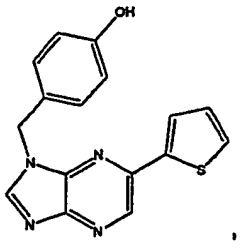
R_6, R_7 and R_8 are independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl, alkynyl, aryl, heteroaryl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl; or

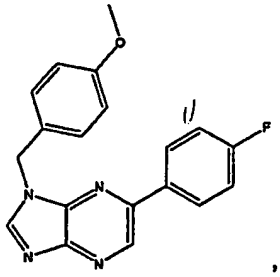
R_7 and R_8 together with the atom to which they are attached form a heteroalicyclic ring optionally substituted with a group selected from the group consisting of alkyl, -OH, amino, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, and dialkylaminoalkyl; and

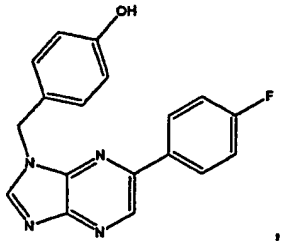
n is 0, 1, 2 or 3, it being understood that when n is greater than 1, the R_1 and R_2 groups on each carbon atom may be the same as or different from the R_1 and R_2 groups on any adjacent carbon atom;

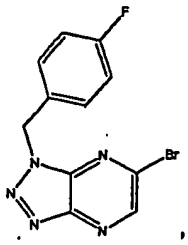
or a pharmaceutically acceptable salt thereof.

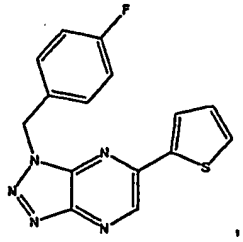
[0022] In a third aspect, the invention relates to a compound of the first or second aspects, which is selected from the group consisting of:

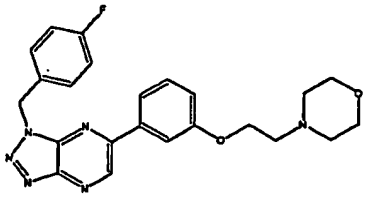


,


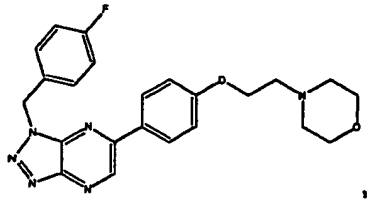
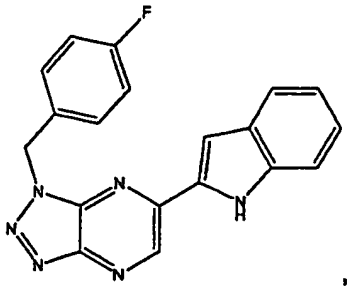
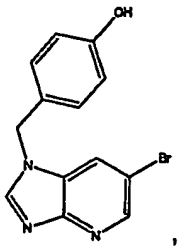
,


,


,


,


,


,

, and

,

or

a pharmaceutically acceptable salt thereof.

[0023] In a fourth aspect, the invention relates to a method for treating a c-Met related disorder with a compound of the first, second or third aspects of the invention.

[0024] In a preferred embodiment, the c-Met related disorder is a cancer. In another preferred embodiment, the cancer is selected from the group consisting of breast cancer, lung cancer, colorectal cancer, prostate cancer, pancreatic cancer, glioma, liver cancer, gastric cancer, head cancer, neck cancer, melanoma, renal cancer, leukemia, myeloma, and sarcoma.

[0025] In a fifth aspect, the invention relates to a pharmaceutical composition comprising a compound of any one of the first, second or third aspects of the invention, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0026] A family of novel tetracyclic compounds have been discovered which exhibit c-Met modulating ability and have a ameliorating effect against disorders related to abnormal c-Met activity. c-Met is an attractive target from a clinical perspective because: 1) c-Met has been implicated in the growth and metastases of most types of cancer; 2) growth at the secondary site appears to be the rate-limiting step in metastasis; and 3) by the time of diagnosis, it is likely that the disease has already spread.

[0027] c-Met is a receptor tyrosine kinase that is encoded by the Met protooncogene and transduces the biological effects of hepatocyte growth factor (HGF), which is also referred to as scatter factor (SF). Jiang *et al.*, *Crit. Rev. Oncol. Hemtol. 29*: 209-248 (1999). c-Met and HGF are expressed in numerous tissues, although their expression is normally confined predominantly to cells of epithelial and mesenchymal origin, respectively. c-Met and HGF are required for normal mammalian development and have been shown to be important in cell migration, cell proliferation and survival, morphogenic differentiation, and organization of 3-dimensional tubular structures (e.g., renal tubular cells, gland formation, etc.). It is proposed that c-Met-dependent tumor growth, invasion, and dissemination is mediated by these cellular actions. In addition to its effects on epithelial cells, HGF/SF has been reported to be an

angiogenic factor, and c-Met signaling in endothelial cells can induce many of the cellular responses necessary for angiogenesis (proliferation, motility, invasion).

[0028] The c-Met receptor has been shown to be expressed in a number of human cancers. c-Met and its ligand, HGF, have also been shown to be co-expressed at elevated levels in a variety of human cancers (particularly sarcomas). However, because the receptor and ligand are usually expressed by different cell types, c-Met signaling is most commonly regulated by tumor-stroma (tumor-host) interactions. Furthermore, c-Met gene amplification, mutation, and rearrangement have been observed in a subset of human cancers. Families with germline mutations that activate c-Met kinase are prone to multiple kidney tumors as well as tumors in other tissues. Numerous studies have correlated the expression of c-Met and/or HGF/SF with the state of disease progression of different types of cancer (including lung, colon, breast, prostate, liver, pancreas, brain, kidney, ovaries, stomach, skin, and bone cancers). Furthermore, the overexpression of c-Met or HGF have been shown to correlate with poor prognosis and disease outcome in a number of major human cancers including lung, liver, gastric, and breast. The strong correlation of c-Met with the biology of metastasis and invasion and disease pathogenesis comprises a novel mechanism for treatment of metastatic cancers.

[0029] c-Met has been directly implicated in cancers without a successful treatment regimen such as pancreatic cancer, glioma, and hepatocellular carcinoma. A c-Met kinase inhibitor could fill an unmet medical need in the treatment of these cancers.

[0030] These observations suggest that c-Met kinase inhibitors would be an effective treatment for primary tumors that are driven by c-Met, but more importantly, would prevent disseminated micrometastases from growing into life-threatening metastases. Therefore, the utility of a c-Met inhibitor extends to preventative and adjuvant therapy settings. In addition, certain cancers (e.g., papillary renal cell carcinoma, some gastric and lung cancers) can be treated which are believed to be driven by c-Met mutation/genetic alteration and dependent on c-Met for growth and survival. These cancers are expected to be sensitive to treatment.

[0031] Various human cancers are the primary target indication for c-Met antagonists. These cancers include major cancers such as breast, lung, colorectal, prostate; as well as pancreatic cancer, glioma, liver cancer, gastric cancer, head and neck cancers, melanoma, renal cancer, leukemias, myeloma, and sarcomas.

[0032] The compounds presented herein are exemplary only and are not to be construed as limiting the scope of this invention in any manner.

[0033] In one aspect, this invention is directed to a pharmaceutical composition comprising one or more compounds of Formula (I) – (IV) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[0034] It is also an aspect of this invention that a compound described herein, or its salt, might be combined with other chemotherapeutic agents for the treatment of the diseases and

disorders discussed above. For instance, a compound or salt of this invention might be combined with alkylating agents such as fluorouracil (5-FU) alone or in further combination with leukovorin; or other alkylating agents such as, without limitation, other pyrimidine analogs such as UFT, capecitabine, gemcitabine and cytarabine, the alkyl sulfonates, *e.g.*, busulfan (used in the treatment of chronic granulocytic leukemia), improsulfan and piposulfan; aziridines, *e.g.*, benzodepa, carboquone, meturedepa and uredepa; ethyleneimines and methylmelamines, *e.g.*, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylolmelamine; and the nitrogen mustards, *e.g.*, chlorambucil (used in the treatment of chronic lymphocytic leukemia, primary macroglobulinemia and non-Hodgkin's lymphoma), cyclophosphamide (used in the treatment of Hodgkin's disease, multiple myeloma, neuroblastoma, breast cancer, ovarian cancer, lung cancer, Wilm's tumor and rhabdomyosarcoma), estramustine, ifosfamide, novembrichin, prednimustine and uracil mustard (used in the treatment of primary thrombocytosis, non-Hodgkin's lymphoma, Hodgkin's disease and ovarian cancer); and triazines, *e.g.*, dacarbazine (used in the treatment of soft tissue sarcoma).

[0035] Likewise a compound or salt of this invention might be expected to have a beneficial effect in combination with other antimetabolite chemotherapeutic agents such as, without limitation, folic acid analogs, *e.g.* methotrexate (used in the treatment of acute lymphocytic leukemia, choriocarcinoma, mycosis fungiodes breast cancer, head and neck cancer and osteogenic sarcoma) and pteropterin; and the purine analogs such as mercaptopurine and thioguanine which find use in the treatment of acute granulocytic, acute lymphocytic and chronic granulocytic leukemias.

[0036] A compound or salt of this invention might also be expected to prove efficacious in combination with natural product based chemotherapeutic agents such as, without limitation, the vinca alkaloids, *e.g.*, vinblastin (used in the treatment of breast and testicular cancer), vincristine and vindesine; the epipodophylotoxins, *e.g.*, etoposide and teniposide, both of which are useful in the treatment of testicular cancer and Kaposi's sarcoma; the antibiotic chemotherapeutic agents, *e.g.*, daunorubicin, doxorubicin, epirubicin, mitomycin (used to treat stomach, cervix, colon, breast, bladder and pancreatic cancer), dactinomycin, temozolomide, plicamycin, bleomycin (used in the treatment of skin, esophagus and genitourinary tract cancer); and the enzymatic chemotherapeutic agents such as L-asparaginase.

[0037] In addition to the above, a compound or salt of this invention might be expected to have a beneficial effect used in combination with the platinum coordination complexes (cisplatin, *etc.*); substituted ureas such as hydroxyurea; methylhydrazine derivatives, *e.g.*, procarbazine; adrenocortical suppressants, *e.g.*, mitotane, aminoglutethimide; and hormone and hormone antagonists such as the adrenocorticosteriods (*e.g.*, prednisone), progestins (*e.g.*, hydroxyprogesterone caproate); estrogens (*e.g.*, diethylstilbesterol); antiestrogens such

as tamoxifen; androgens, *e.g.*, testosterone propionate; and aromatase inhibitors (such as anastrozole.

[0038] Finally, the combination of a compound of this invention might be expected to be particularly effective in combination with mitoxantrone or paclitaxel for the treatment of solid tumor cancers or leukemias such as, without limitation, acute myelogenous (non-lymphocytic) leukemia.

[0039] The above method can be carried out in combination with a chemotherapeutic agent selected from the group consisting of mitotic inhibitors, alkylating agents, antimetabolites, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, antiangiogenic agents such as MMP-2, MMP-9 and COX-2 inhibitors, and anti-androgens.

[0040] Examples of useful COX-II inhibitors include Vioxx™, CELEBREX™ (alecoxib), valdecoxib, paracoxib, rofecoxib, and Cox 189. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published Oct. 24, 1996), WO 96/27583 (published Mar. 7, 1996), European Patent Application No. 97304971.1 (filed Jul. 8, 1997), European Patent Application No. 99308617.2 (filed Oct. 29, 1999), WO 98/07697 (published Feb. 26, 1998), WO 98/03516 (published Jan. 29, 1998), WO 98/34918 (published Aug. 13, 1998), WO 98/34915 (published Aug. 13, 1998), WO 98/33768 (published Aug. 6, 1998), WO 98/30566 (published Jul. 16, 1998), European Patent Publication 606,046 (published Jul. 13, 1994), European Patent Publication 931,788 (published Jul. 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published Oct. 21, 1999), WO 99/52889 (published Oct. 21, 1999), WO 99/29667 (published Jun. 17, 1999), PCT International Application No. PCT/IB98/01113 (filed Jul. 21, 1998), European Patent Application No. 99302232.1 (filed Mar. 25, 1999), Great Britain patent application number 9912961.1 (filed Jun. 3, 1999), U.S. Provisional Application No. 60/148,464 (filed Aug. 12, 1999), U.S. Pat. No. 5,863,949 (issued Jan. 26, 1999), U.S. Pat. No. 5,861,510 (issued Jan. 19, 1999), and European Patent Publication 780,386 (published Jun. 25, 1997), all of which are incorporated herein in their entireties by reference.

[0041] Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (i.e. MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13). Some specific examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, RS 13-0830, and the compounds recited in the following list:

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)- amino]-propionic acid; 3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(2-chloro-4-fluoro-benzyloxy)-

benzenesulfonyl]-3-hydroxy-3-methyl-pip eridine-2-carboxylic acid hydroxyamide; 4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclobutyl)-a mino]-propionic acid; 4-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide; (R) 3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-3-carboxyli c acid hydroxyamide; (2R, 3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-pip eridine-2-carboxylic acid hydroxyamide; 3-[[(4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-1-methyl-ethyl)-amino]-propionic acid; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro-py ran-4-yl)-amino]-propionic acid; 3-exo-3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2. 1]octane-3-carboxylic acid hydroxyamide; 3-endo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2. 1]octane-3-carboxylic acid hydroxyamide; and (R) 3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-furan-3-carboxyli c acid hydroxyamide; and pharmaceutically acceptable salts and solvates of said compounds.

[0042] Other anti-angiogenesis agents, including other COX-II inhibitors and other MMP inhibitors, can also be used in the present invention.

[0043] Compounds of the Formulae (I) – (IV) can also be used with signal transduction inhibitors, such as agents that can inhibit EGFR (epidermal growth factor receptor) responses, such as EGFR antibodies, EGF antibodies, and molecules that are EGFR inhibitors; VEGF (vascular endothelial growth factor) inhibitors; and erbB2 receptor inhibitors, such as organic molecules or antibodies that bind to the erbB2 receptor, for example, HERCEPTIN.TM. (Genentech, Inc. of South San Francisco, Calif., USA). EGFR inhibitors are described in, for example in WO 95/19970 (published Jul. 27, 1995), WO 98/14451 (published Apr. 9, 1998), WO 98/02434 (published Jan. 22, 1998), and U.S. Pat. No. 5,747,498 (issued May 5, 1998), and such substances can be used in the present invention as described herein.

[0044] EGFR-inhibiting agents include, but are not limited to, the monoclonal antibodies C225 and anti-EGFR 22Mab (ImClone Systems Incorporated of New York, N.Y., USA), the compounds ZD-1839 (AstraZeneca), BIBX-1382 (Boehringer Ingelheim), MDX-447 (Medarex Inc. of Annandale, N.J., USA), and OLX-103 (Merck & Co. of Whitehouse Station, N.J., USA), VRCTC-310 (Ventech Research) and EGF fusion toxin (Seragen Inc. of Hopkinton, Mass.).

[0045] These and other EGFR-inhibiting agents can be used in the present invention.

[0046] VEGF inhibitors, for example SU-5416, SU 11248, SU-6668 (Sugen Inc. of South San Francisco, Calif., USA), can also be combined with a compounds of the Formulae (I) – (IV). VEGF inhibitors are described in, for example in WO 99/24440 (published May 20, 1999), PCT International Application PCT/IB99/00797 (filed May 3, 1999), in WO 95/21613 (published Aug. 17,1995), WO 99/61422 (published Dec. 2,1999), U.S. Pat. No. 5,834,504 (issued Nov. 10, 1998), WO 01/60814,WO 98/50356 (published Nov. 12, 1998), U.S. Pat. No. 5,883,113 (issued Mar. 16, 1999), U.S. Pat. No. 5,886,020 (issued Mar. 23, 1999), U.S. Pat.

No. 5,792,783 (issued Aug. 11, 1998), WO 99/10349 (published Mar. 4, 1999), WO 97/32856 (published Sep. 12, 1997), WO 97/22596 (published Jun.26, 1997), WO 98/54093 (published Dec. 3, 1998), WO 98/02438 (published Jan. 22, 1998), WO 99/16755 (published Apr. 8, 1999), and WO 98/02437 (published Jan. 22, 1998), all of which are incorporated herein in their entireties by reference. Other examples of some specific VEGF inhibitors useful in the present invention are IM862 (Cytran Inc. of Kirkland, Wash., USA); anti-VEGF monoclonal antibody of Genentech, Inc. of South San Francisco, Calif.; and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colo.) and Chiron (Emeryville, Calif.). These and other VEGF inhibitors can be used in the present invention as described herein.

[0047] ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc. of TheWoodlands, Tex., USA) and 2B-1 (Chiron), can furthermore be combined with a compound of the Formula (I) – (IV) for example those indicated in WO 98/02434 (published Jan. 22, 1998), WO 99/35146 (published Jul. 15, 1999), WO 99/35132 (published Jul. 15, 1999), WO 98/02437 (published Jan. 22, 1998), WO 97/13760 (published Apr. 17, 1997), WO 95/19970 (published Jul. 27, 1995), U.S. Pat. No. 5,587,458 (issued Dec. 24, 1996), and U.S. Pat. No. 5,877,305 (issued Mar. 2, 1999), which are all hereby incorporated herein in their entireties by reference. ErbB2 receptor inhibitors useful in the present invention are also described in U.S. Provisional Application No. 60/117,341, filed Jan. 27, 1999, and in U.S. Provisional Application No. 60/117,346, filed Jan. 27,1999, both of which are incorporated in their entireties herein by reference. The erbB2 receptor inhibitor compounds and substance described in the aforementioned PCT applications, U.S. patents, and U.S. provisional applications, as well as other compounds and substances that inhibit the erbB2 receptor, can be used with compounds of the Formulae (I) – (IV), in accordance with the present invention.

[0048] Compounds of the Formula (I) – (IV) can also be used with other agents useful in treating cancer, including, but not limited to, agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocite antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents such as other farnesyl protein transferase inhibitors, for example the farnesyl protein transferase inhibitors described in the references cited in the "Background" section, of US Patent No, 6,258,824 B1. Specific CTLA4 antibodies that can be used in the present invention include those described in U.S. Provisional Application 60/113,647 (filed Dec. 23, 1998) which is incorporated by reference in its entirety, however other CTLA4 antibodies can be used in the present invention.

[0049] The above method can be also be carried out in combination with radiation therapy, wherein the amount of a compound of the Formula (I) – (IV) in combination with the radiation therapy, is effective in treating the above diseases. The level of radiation therapy administered may be reduced to a sub-efficacy dose when administered in combination with the compounds of the preferred embodiments of the present invention.

[0050] Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound of the invention in this combination therapy can be determined as described herein.

[0051] Another aspect of the invention is directed ot the use of compounds of the Formulae (I) – (IV) in the preparation of a medicament, which is useful in the treatment of a disease *mediated by abnormal Met kinase activity.*

[0052] "Pharmaceutically acceptable salt" or "pharmaceutically acceptable salt thereof" refer to those salts which retain the biological effectiveness and properties of the free bases and which are obtained by reaction with inorganic or organic acids, such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, acetic acid, benzenesulfonic acid (besylate), benzoic acid, camphorsulfonic acid, citric acid, fumaric acid, gluconic acid, glutamic acid, isethionic acid, lactic acid, maleic acid, malic acid, mandelic acid, mucic acid, pamoic acid, pantothenic acid, succinic acid, tartaric acid, and the like.

[0053] A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or physiologically acceptable salts thereof, with other chemical components, such as physiologically acceptable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

[0054] As used herein, a "physiologically acceptable carrier" refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

[0055] An "excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound. Examples, without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives (including microcrystalline cellulose), gelatin, vegetable oils, polyethylene glycols, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like.

[0056] "Alkyl" refers to a saturated aliphatic hydrocarbon including straight chain, branched chain or cyclic groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever a numerical range; *e.g.*, "1-20", is stated herein, it means that the group, in this case the alkyl group, may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.* up to and including 20 carbon atoms). More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, each substituent group is preferably one or more individually selected from halogen, -hydroxy, -COR', -COOR', OCOR', -CONRR', -RNCOR', -NRR', -CN, $-NO_2$, $-CZ_3$, -SR', -SOR', $-SO_2R'$, $-SO_2OR'$, $-SO_2NRR'$, thiocarbonyl, $-RNSO_2R'$, perfluoroalkyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, silyl,

ammonium, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heteroalicycle, heteroaryl and aryl. R and R' are independently H, alkyl, or aryl, wherein alkyl or aryl may be further substituted with halogen, $(CH_2)_nN(R'')_2$, $(CH_2)_nCO_2R''$, $(CH_2)_nOR''$, $(CH_2)_nOC(O)R''$, alkoxycarbonyl, aryloxycarbonyl, aminocarbonyl, a heteroalicyclic ring, aryl, alkoxy, $-OCZ_3$, aryloxy, $C(O)NH_2$ or heteroaryl. R'' is H, alkyl or aryl. n is 0 - 3.

[0057] "Alkenyl" refers to an aliphatic hydrocarbon having at least one carbon-carbon double bond, including straight chain, branched chain or cyclic groups having at least one carbon-carbon double bond. Preferably, the alkenyl group has 2 to 20 carbon atoms (whenever a numerical range; *e.g.*, "2-20", is stated herein, it means that the group, in this case the alkenyl group, may contain 2 carbon atoms, 3 carbon atoms, *etc.* up to and including 20 carbon atoms). More preferably, it is a medium size alkenyl having 2 to 10 carbon atoms. Most preferably, it is a lower alkenyl having 2 to 6 carbon atoms. The alkenyl group may be substituted or unsubstituted. When substituted, each substituent group is preferably one or more individually selected from halogen, -hydroxy, -COR', -COOR', OCOR', -CONRR', -RNCOR', -NRR', -CN, $-NO_2$, $-CZ_3$, -SR', -SOR', $-SO_2R'$, $-SO_2OR'$, $-SO_2NRR'$, thiocarbonyl, $-RNSO_2R'$, perfluoroalkyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, silyl, ammonium, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heteroalicycle, heteroaryl and aryl. Wherein R and R' are defined herein.

[0058] "Alkynyl" refers to an aliphatic hydrocarbon having at least one carbon-carbon triple bond, including straight chain, branched chain or cyclic groups having at least one carbon-carbon triple bond. Preferably, the alkenyl group has 2 to 20 carbon atoms (whenever a numerical range; *e.g.*, "2-20", is stated herein, it means that the group, in this case the alkynyl group, may contain 2 carbon atoms, 3 carbon atoms, *etc.* up to and including 20 carbon atoms). More preferably, it is a medium size alkynyl having 2 to 10 carbon atoms. Most preferably, it is a lower alkynyl having 2 to 6 carbon atoms. The alkynyl group may be substituted or unsubstituted. When substituted, each substituent group is preferably one or more individually selected from halogen, -hydroxy, -COR', -COOR', OCOR', -CONRR', -RNCOR', -NRR', -CN, $-NO_2$, $-CZ_3$, -SR', -SOR', $-SO_2R'$, $-SO_2OR'$, $-SO_2NRR'$, thiocarbonyl, $-RNSO_2R'$, perfluoroalkyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, silyl, ammonium, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heteroalicycle, heteroaryl and aryl. Wherein R and R' are defined herein.

[0059] A "cycloalkyl" or an "alicyclic" group refers to an all-carbon monocyclic or fused ring (*i.e.*, rings which share an adjacent pair of carbon atoms) group wherein one of more of the rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, adamantane, cyclohexadiene, cycloheptane and, cycloheptatriene. A cycloalkyl group may be substituted or unsubstituted. When substituted, each substituent group is

preferably one or more individually selected from halogen, -hydroxy, -COR', -COOR', OCOR', -CONRR', -RNCOR', -NRR', -CN, -NO_2, -CZ_3, -SR', -SOR', -SO_2R', -SO_2OR', -SO_2NRR', thiocarbonyl, -$RNSO_2R'$, perfluoroalkyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, silyl, ammonium, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heteroalicycle, heteroaryl and aryl. Wherein R and R' are defined herein.

[0060] An "aryl" group refers to an all-carbon monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. When substituted, each substituted group is preferably one or more selected halogen, hydroxy, alkoxy, aryloxy,-COR', -COOR', OCOR', -CONRR', -RNCOR', -NRR', -CN, -NO_2, -CZ_3, -OCZ_3, -SR', -SOR', -SO_2R', -SO_2OR', -SO_2NRR', thiocarbonyl, -$RNSO_2R'$, perfluoroalkyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, silyl, ammonium, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heteroalicycle, heteroaryl and aryl. Wherein R and R' are defined herein.

[0061] As used herein, a "heteroaryl" group refers to a monocyclic or fused ring (*i.e.*, rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Examples, without limitation, of heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, isoquinoline, purine and carbazole. The heteroaryl group may be substituted or unsubstituted. When substituted, each substituted group is preferably one or more selected from halogen, -hydroxy, -COR', -COOR', OCOR' , -CONRR', -RNCOR', -NRR', -CN, -NO_2, -CZ_3, -SR', -SOR', -SO_2R', -SO_2OR', -SO_2NRR', thiocarbonyl, -$RNSO_2R'$, perfluoroalkyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, silyl, ammonium, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heteroalicycle, heteroaryl and aryl, where Z is halogen. Wherein R and R' are defined herein.

[0062] A "heteroalicyclic ring" or "heteroalicycle" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. The rings may also have one or more double bonds. However, the rings may not have a completely conjugated pi-electron system. The heteroalicyclic ring may be substituted or unsubstituted. The heteroalicyclic ring may contain one or more oxo groups. When substituted, the substituted group(s) is preferably one or more selected halogen, hydroxy, -COR', -COOR', OCOR', -CONRR', -RNCOR', -NRR', -CN, -NO_2, -CZ_3, -SR', -SOR', -SO_2R', -SO_2OR', -SO_2NRR', thiocarbonyl, -$RNSO_2R'$, perfluoroalkyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, silyl, ammonium, lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl, heteroalicycle, heteroaryl and aryl. Wherein R and R' are defined herein.

[0063] Z refers to a halogen group selected from the group consisting of fluorine, chlorine, bromine and iodine.

[0064] A "hydroxy" group refers to an –OH group.

[0065] An "alkoxy" group refers to both an –O-alkyl and an –O-cycloalkyl group, as defined herein.

[0066] An "alkoxycarbonyl" refers to a –C(O)-OR.

[0067] An "aminocarbonyl" refers to a –C(O)-NRR'.

[0068] An "aryloxycarbonyl" refers to –C(O)-Oaryl.

[0069] An "aryloxy" group refers to both an –O-aryl and an –O-heteroaryl group, as defined herein.

[0070] An "arylalkyl" group refers to –alkyl-aryl, where alkyl and aryl are defined herein.

[0071] An "arylsulfonyl" group refers to a $-SO_2$-aryl.

[0072] An "alkylsulfonyl" group refer to a $-SO_2$-alkyl.

[0073] A "heteroaryloxyl" group refers to a heteroaryl–O– group with heteroaryl as defined herein.

[0074] A "heteroalicycloxy" group refers to a heteroalicyclic-O– group with heteroalicyclic as defined herein.

[0075] A "carbonyl" group refers to a –C(=O)-R.

[0076] An "aldehyde" group refers to a carbonyl group where R is hydrogen.

[0077] A "thiocarbonyl" group refers to a –C(=S)–R group.

[0078] A "trihalomethanecarbonyl" group refers to a Z_3C-C(O)– group.

[0079] A "C-carboxyl" group refers to a –C(O)O–R groups.

[0080] An "O-carboxyl" group refers to a R–C(O)O– group.

[0081] A "carboxylic acid" group refers to a C-carboxyl group in which R is hydrogen.

[0082] A "halo" or "halogen" group refers to fluorine, chlorine, bromine or iodine.

[0083] A "trihalomethyl" group refers to a – CZ_3 group.

[0084] A "trihalomethanesulfonyl" group refers to a $Z_3CS(O)_2$ group.

[0085] A "trihalomethanesulfonamido" group refers to a $Z_3CS(O)_2NR$– group.

[0086] A "sulfinyl" group refers to a –S(O)–R group.

[0087] A "sulfonyl" group refers to a $-S(O)_2R$ group.

[0088] An "S-sulfonamido" group refers to a $-S(O)_2NR$— group.

[0089] An "N-Sulfonamido" group refers to a –NR–$S(O)_2$ R group.

[0090] An "O-carbamyl" group refers to a –OC(O)NRR' group.

[0091] An "N-carbamyl" group refers to a ROC(O)NR— group.

[0092] An "O-thiocarbamyl" group refers to a –OC(S)NRR' group.

[0093] An "N-thiocarbamyl" group refers to a ROC(S)NR'– group.

[0094] An "amino" group refers to an $-NH_2$ or an –NRR'group.

[0095] A "C-amido" group refers to a –C(O)NRR' group.

[0096] An "N-amido" group refers to a R'C(O)NR– group.

[0097] A "nitro" group refers to a $-NO_2$ group.

[0098] A "cyano" group refers to a –CN group.

[0099] A "silyl" group refers to a $-Si(R)_3$ group.

[0100] A "phosphonyl" group refers to a $P(=O)(OR)_2$ group.

[0101] An "aminoalkyl" group refers to an –alkylNRR' group.

[0102] An "alkylaminoalkyl" group refers to an –alkyl—NR—alkyl group.

[0103] A "dialkylamionalkyl" group refers to an –alkyl—N—$(alkyl)_2$ group.

[0104] A "perfluoroalkyl group" refers to an alkyl group where all of the hydrogen atoms have been replaced with fluorine atoms.

[0105] The definitions of $R_1 - R_{13}$, X, Y, R, R' and R" are defined in the present specification.

[0106] Compounds that have the same molecular formula but difer in the nature or sequence of bonding of their atoms or arrangements of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture". The chemical formulae referred to herein may exhibit the phenomena of tautomerism and structural isomerism. This invention encompasses any tautomeric or structural isomeric form and mixtures thereof which possess the ability to modulate c-Met activity and is not limited to any one tautomeric or structural isomeric form. This invention encompasses any tautomeric or structural isomeric form and mixtures thereof which possess the ability to modulate c-Met activity and is not limited to any one tautomeric or structural isomeric form.

[0107] The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)- stereoisomers or as mixtures thereof. For example, if the R_1 and R_2 substituents in a compound of Formula (I) are different, then that carbon is an asymmetric center. Thus, the compound of Formula (I) can

exist as an (R)- or (S)-stereoisomer. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 1992). Thus, this invention also encompasses any stereoisomeric form, their corresponding enantiomers (d- and 1- or (+) and (-) isomers) and diastereomers thereof, and mixtures thereof, which possess the ability to modulate c-Met activity and is not limited to any one stereoisomeric form.

[0108] The compounds of the Formulae (I) – (IV) may exhibit the phenomena of tautomerism and structural isomerism. For example, the compounds described herein may adopt an E or a Z configuration about a double bond or they may be a mixture of E and Z. This invention encompasses any tautomeric or structural isomeric form and mixtures thereof which possess the ability to modulate c-Met activity and is not limited to any one tautomeric or structural isomeric form.

[0109] It is contemplated that compounds of the Formula (I) – (IV) would be metabolized by enzymes in the body of the organism such as human being to generate a metabolite that can modulate the activity of c-Met. Such metabolites are within the scope of the present invention.

[0110] The term "method" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by, practitioners of the chemical, pharmaceutical, biological, biochemical and medical arts.

[0111] As used herein, the term "modulation" or "modulating" refers to the alteration of the catalytic activity of c-Met. In particular, modulating refers to the activation of the catalytic activity of c-Met, preferably the activation or inhibition of the catalytic activity of c-Met, depending on the concentration of the compound or salt to which c-Met is exposed or, more preferably, the inhibition of the catalytic activity of c-Met.

[0112] The term "contacting" as used herein refers to bringing a compound of this invention and c-Met together in such a manner that the compound can affect the catalytic activity of c-Met, either directly, *i.e.*, by interacting with c-Met itself, or indirectly, *i.e.*, by interacting with another molecule on which the catalytic activity of c-Met is dependent. Such "contacting" can be accomplished *in vitro*, *i.e.*, in a test tube, a petri dish or the like. In a test tube, contacting may involve only a compound and c-Met or it may involve whole cells. Cells may also be maintained or grown in cell culture dishes and contacted with a compound in that environment. In this context, the ability of a particular compound to affect a c-Met related

disorder, *i.e.*, the IC_{50} of the compound, defined below, can be determined before use of the compounds *in vivo* with more complex living organisms is attempted. For cells outside the organism, multiple methods exist, and are well-known to those skilled in the art, to get c-Met in contact with the compounds including, but not limited to, direct cell microinjection and numerous transmembrane carrier techniques.**[0113]** "*In vitro*" refers to procedures performed in an artificial environment such as, *e.g.*, without limitation, in a test tube or culture medium. The skilled artisan will understand that, for example, isolated c-Met may be contacted with a modulator in an *in vitro* environment. Alternatively, an isolated cell may be contacted with a modulator in an *in vitro* environment.

[0114] As used herein, "*in vivo*" refers to procedures performed within a living organism such as, without limitation, a mouse, rat, rabbit, ungulate, bovine, equine, porcine, canine, feline, primate, or human.

[0115] As used herein, "c-Met related disorder," refers to a condition characterized by inappropriate, *i.e.*, under-activity or, more commonly, over-activity of the c-Met catalytic activity. A "c-Met related disorder" also refers to a condition where there may be a mutation in the gene that produces c-Met, which, in turn, produces a c-Met that has an increased or decreased c-Met catalytic activity.

[0116] Inappropriate catalytic activity can arise as the result of either: (1) c-Met expression in cells which normally do not express c-Met, (2) increased c-Met expression leading to unwanted cell proliferation, differentiation and/or growth, or, (3) decreased c-Met expression leading to unwanted reductions in cell proliferation, differentiation and/or growth. Over-activity of a c-Met refers to either amplification of the gene encoding a c-Met or production of a level of c-Met activity which can correlate with a cell proliferation, differentiation and/or growth disorder (that is, as the level of the c-Met increases, the severity of one or more of the symptoms of the cellular disorder increases). Under-activity is, of course, the converse, wherein the severity of one or more symptoms of a cellular disorder increase as the level of the c-Met activity decreases.

[0117] As used herein, the terms "prevent", "preventing" and "prevention" refer to a method for barring an organism from acquiring a c-Met related disorder in the first place.

[0118] As used herein, the terms "treat", "treating" and "treatment" refer to a method of alleviating or abrogating a c-Met mediated cellular disorder and/or its attendant symptoms. With regard particularly to cancer, these terms simply mean that the life expectancy of an individual affected with a cancer will be increased or that one or more of the symptoms of the disease will be reduced.

[0119] The term "organism" refers to any living entity comprised of at least one cell. A living organism can be as simple as, for example, a single eukaryotic cell or as complex as a

mammal. In a preferred aspect, the organism is a mammal. In a particularly preferred aspect, the mammal is a human being.

[0120] The term "therapeutically effective amount" as used herein refers to that amount of the compound being administered which will relieve to some extent one or more of the symptoms of the disorder being treated. In reference to the treatment of cancer, a therapeutically effective amount refers to that amount which has the effect of (1) reducing the size of the tumor, (2) inhibiting (that is, slowing to some extent, preferably stopping) tumor metastasis, (3) inhibiting to some extent (that is, slowing to some extent, preferably stopping) tumor growth, and/or, (4) relieving to some extent (or, preferably, eliminating) one or more symptoms associated with the cancer.

[0121] By "monitoring" is meant observing or detecting the effect of contacting a compound with a cell expressing a c-Met. The observed or detected effect can be a change in cell phenotype, in the catalytic activity of c-Met or a change in the interaction of c-Met with a natural binding partner. Techniques for observing or detecting such effects are well-known in the art. For example, the catalytic activity of c-Met may be observed by determining the rate or amount of phosphorylation of a target molecule.

[0122] "Cell phenotype" refers to the outward appearance of a cell or tissue or the biological function of the cell or tissue. Examples, without limitation, of a cell phenotype are cell size, cell growth, cell proliferation, cell differentiation, cell survival, apoptosis, and nutrient uptake and use. Such phenotypic characteristics are measurable by techniques well-known in the art.

[0123] A "natural binding partner" refers to a polypeptide that binds to a c-Met in a cell. Natural binding partners can play a role in propagating a signal in a c-Met-mediated signal transduction process. A change in the interaction of the natural binding partner with c-Met can manifest itself as an increased or decreased concentration of the c-Met/natural binding partner complex and, as a result, in an observable change in the ability of c-Met to mediate signal transduction.

[0124] As used herein, "administer" or "administration" refers to the delivery of a compound or salt of the present invention or of a pharmaceutical composition containing a compound or salt of this invention to an organism for the purpose of prevention or treatment of a c-Met-related disorder.

[0125] A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or pharmaceutically acceptable salts or prodrugs thereof, with other chemical components, such as pharmaceutically acceptable excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

[0126] "Pharmaceutically acceptable excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound. Examples,

without limitation, of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils and polyethylene glycols.

[0127] "Pharmaceutically acceptable salt" refers to those salts, which retain the biological effectiveness and properties of the parent compound. Such salts include:

[0128] (1) acid addition salt which is obtained by reaction of the free base of the parent compound with inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, phosphoric acid, sulfuric acid, and perhcloric acid and the like, or with organic acids such as acetic acid, oxalic acid, (D) or (L) malic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, tartaric acid, citric acid, succinic acid or malonic acid and the like, preferably hydrochloric acid or (L)-malic acid; or

[0129] (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[0130] The compounds of the Formulae (I) – (IV) may also act as prodrugs. A "prodrug" refers to an agent, which is converted into the parent drug *in vivo*. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. An example, without limitation, of a prodrug would be a compound of the present invention, which is, administered as an ester (the "prodrug"), carbamate or urea.

Indications

[0131] A precise understanding of the mechanism by which the compounds of the invention, in particular, the compounds generated *in vivo* from the compounds of the invention, inhibit c-Met is not required in order to practice the present invention. However, while not hereby being bound to any particular mechanism or theory, it is believed that the compounds interact with the amino acids in the catalytic region of c-Met. The compounds disclosed herein may thus have utility as *in vitro* assays for c-Met as well as exhibiting *in vivo* therapeutic effects through interaction with c-Met.

[0132] In another aspect, this invention relates to a method for treating or preventing a c-Met related disorder by administering a therapeutically effective amount of a compound of this invention, or a salt thereof, to an organism.

[0133] It is also an aspect of this invention that a pharmaceutical composition containing a compound of this invention, or a salt thereof, is administered to an organism for the purpose of preventing or treating a c-Met related disorder.

[0134] This invention is therefore directed to compounds that modulate PK signal transduction by affecting the enzymatic activity of c-Met, thereby interfering with the signal transduced by c-Met. More particularly, the present invention is directed to compounds which

modulate c-Met mediated signal transduction pathways as a therapeutic approach to treat the many cancers described herein.

[0135] A method for identifying a chemical compound that modulates the catalytic activity of c-Met is another aspect of this invention. The method involves contacting cells expressing c-Met with a compound of this invention (or its salt) and monitoring the cells for any effect that the compound has on them. Alternatively, the method can involve contacting the c-Met protein itself (i.e., not in a cell) with a chemical compound of the preferred embodiments of the present invention and monitoring the protein for any effect that the compound has on it. The effect may be observable, either to the naked eye or through the use of instrumentation. The effect may be, for example, a change or absence in a cell phenotype. The change or absence of change in the cell phenotype monitored, for example, may be, without limitation, a change or absence of change in the catalytic activity of c-Met in the cells or a change or absence of change in the interaction of c-Met with a natural binding partner.

Pharmaceutical Compositions and Use

[0136] A compound of the present invention or a physiologically acceptable salt thereof, can be administered as such to a human patient or can be administered in pharmaceutical compositions in which the foregoing materials are mixed with suitable carriers or excipient(s). Techniques for formulation and administration of drugs may be found in "Remington's Pharmacological Sciences," Mack Publishing Co., Easton, PA, latest edition.

Routes of Administration

[0137] Suitable routes of administration may include, without limitation, oral, intraoral, rectal, transmucosal or intestinal administration or intramuscular, epicutaneous, parenteral, subcutaneous, transdermal, intramedullary, intrathecal, direct intraventricular, intravenous, intravitreal, intraperitoneal, intranasal, intramuscular, intradural, intrarespiratory, nasal inhalation or intraocular injections. The preferred routes of administration are oral and parenteral.

[0138] Alternatively, one may administer the compound in a local rather than systemic manner, for example, *via* injection of the compound directly into a solid tumor, often in a depot or sustained release formulation.

[0139] Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with tumor-specific antibody. The liposomes will be targeted to and taken up selectively by the tumor.

Composition/Formulation

[0140] Pharmaceutical compositions of the present invention may be manufactured by processes well known in the art, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, lyophilizing processes or spray drying.

[0141] Pharmaceutical compositions for use in the methods of the present invention may be prepared by any methods of pharmacy, but all methods include the step of bringing in association the active ingredient with the carrier which constitutes one or more necessary ingredients. In particular, pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[0142] Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches, syrups, elixirs, gels, powders, magmas, lozenges, ointments, creams, pastes, plasters, lotions, discs, suppositories, nasal or oral sprays, aerosols and the like.

[0143] For injection, the compounds of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such buffers with or without a low concentration of surfactant or cosolvent, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0144] For oral administration, the compounds can be formulated by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, lozenges, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient. Pharmaceutical preparations for oral use can be made using a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding other suitable auxiliaries if desired, to obtain tablets or dragee cores. Useful excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol, cellulose preparations such as, for example, maize starch, wheat starch, rice starch and potato starch and other materials such as gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinyl- pyrrolidone (PVP). If desired, disintegrating agents may be added, such as cross-linked polyvinyl pyrrolidone, agar, or alginic acid. A salt such as sodium alginate may also be used.

[0145] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0146] Pharmaceutical compositions which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with

a filler such as lactose, a binder such as starch, and/or a lubricant such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, liquid polyethylene glycols, cremophor, capmul, medium or long chain mono- di- or triglycerides. Stabilizers may be added in these formulations, also.

[0147] For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray using a pressurized pack or a nebulizer and a suitable propellant, *e.g.*, without limitation, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra- fluoroethane or carbon dioxide. In the case of a pressurized aerosol, the dosage unit may be controlled by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0148] The compounds may also be formulated for parenteral administration, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating materials such as suspending, stabilizing and/or dispersing agents.

[0149] Pharmaceutical compositions for parenteral administration include aqueous solutions of a water soluble form, such as, without limitation, a salt, of the active compound. Additionally, suspensions of the active compounds may be prepared in a lipophilic vehicle. Suitable lipophilic vehicles include fatty oils such as sesame oil, synthetic fatty acid esters such as ethyl oleate and triglycerides, or materials such as liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers and/or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0150] Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, *e.g.*, sterile, pyrogen-free water, before use.

[0151] The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, using, *e.g.*, conventional suppository bases such as cocoa butter or other glycerides.

[0152] In addition to the formulations described previously, the compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. A compound of this invention may be formulated for this route of administration with suitable polymeric or hydrophobic materials (for instance, in an emulsion with a pharmacologically

acceptable oil), with ion exchange resins, or as a sparingly soluble derivative such as, without limitation, a sparingly soluble salt.

[0153] A non-limiting example of a pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer and an aqueous phase such as the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:D5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of such a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of Polysorbate 80, the fraction size of polyethylene glycol may be varied, other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone, and other sugars or polysaccharides may substitute for dextrose.

[0154] Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. In addition, certain organic solvents such as dimethylsulfoxide also may be employed, although often at the cost of greater toxicity.

[0155] Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

[0156] The pharmaceutical compositions herein also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, but are not limited to, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[0157] Many of the PK modulating compounds of the invention may be provided as physiologically acceptable salts wherein the claimed compound may form the negatively or the positively charged species. Examples of salts in which the compound forms the positively charged moiety include, without limitation, quaternary ammonium (defined elsewhere herein), salts such as the hydrochloride, sulfate, carbonate, lactate, tartrate, maleate, succinate, malate, acetate and methylsulfonate (CH_3SO_3), wherein the nitrogen atom of the quaternary ammonium group is a nitrogen of the selected compound of this invention which has reacted

with the appropriate acid. Salts in which a compound of this invention forms the negatively charged species include, without limitation, the sodium, potassium, calcium and magnesium salts formed by the reaction of a carboxylic acid group in the compound with an appropriate base (*e.g.* sodium hydroxide (NaOH), potassium hydroxide (KOH), Calcium hydroxide ($Ca(OH)_2$), *etc.*).

Dosage

[0158] Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an amount sufficient to achieve the intended purpose, *i.e.*, the modulation of PK activity or the treatment or prevention of a PK-related disorder.

[0159] More specifically, a therapeutically effective amount means an amount of compound effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

[0160] Determination of a therapeutically effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0161] For any compound used in the methods of the invention, the therapeutically effective amount or dose can be estimated initially from cell culture assays. Then, the dosage can be formulated for use in animal models so as to achieve a circulating concentration range that includes the IC_{50} as determined in cell culture *(i.e.,* the concentration of the test compound which achieves a half-maximal inhibition of c-Met activity). Such information can then be used to more accurately determine useful doses in humans.

[0162] Toxicity and therapeutic efficacy of the compounds described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, by determining the IC_{50} and the LD_{50} (both of which are discussed elsewhere herein) for a subject compound. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage may vary depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See *e.g.*, Fingl, *et al.*, 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p.1).

[0163] Dosage amount and interval may be adjusted individually to provide plasma levels of the active species which are sufficient to maintain the kinase modulating effects. These plasma levels are referred to as minimal effective concentrations (MECs). The MEC will vary for each compound but can be estimated from *in vitro* data, *e.g.*, the concentration necessary to achieve 50-90% inhibition of a kinase may be ascertained using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and

route of administration. HPLC assays or bioassays can be used to determine plasma concentrations.

[0164] Dosage intervals can also be determined using MEC value. Compounds should be administered using a regimen that maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90%. At present, the therapeutically effective amounts of compounds of the Formulae (I) – (IV) may range from approximately 10 mg/m^2 to 1000 mg/m^2 perday. Even more preferably 25 mg/m^2 to 500 mg/m^2.

[0165] In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration and other procedures known in the art may be employed to determine the correct dosage amount and interval.

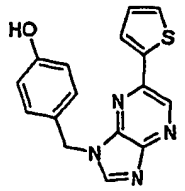
[0166] The amount of a composition administered will, of course, be dependent on the subject being treated, the severity of the affliction, the manner of administration, the judgment of the prescribing physician, *etc.*

Packaging

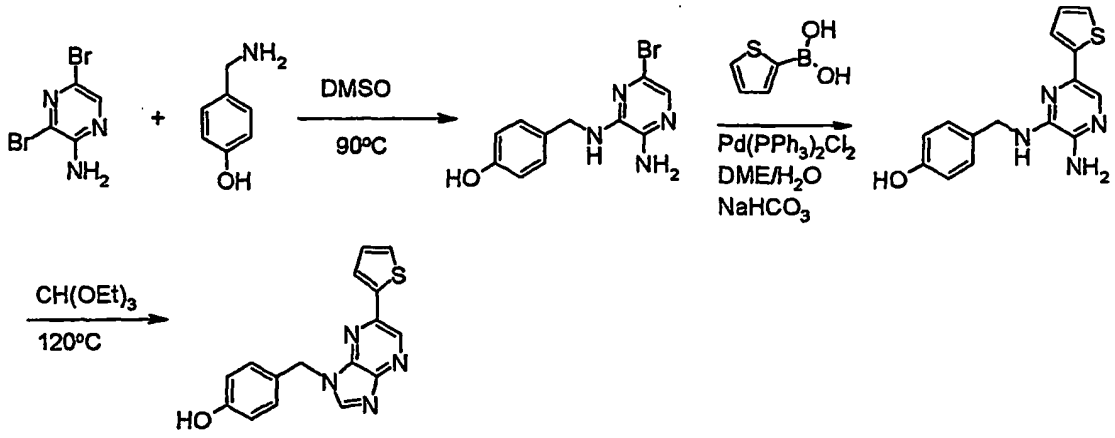
[0167] The compositions may, if desired, be presented in a pack or dispenser device, such as an FDA approved kit, which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied by a notice associated with the container in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the compositions or of human or veterinary administration. Such notice, for example, may be of the labeling approved by the U.S. Food and Drug Administration for prescription drugs or of an approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition. Suitable conditions indicated on the label may include treatment of a tumor, inhibition of angiogenesis, treatment of fibrosis, diabetes, and the like.

EXAMPLES

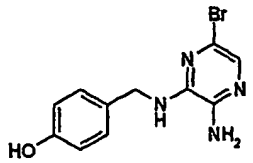
Example 1. 4-(6-Thiophen-2-yl-imidazo[4,5-b]pyrazin-1-ylmethyl)-phenol



Synthetic Scheme I:



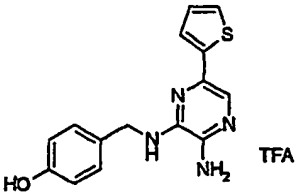
Step 1: Preparation of 4-[(3-amino-6-bromo-pyrazin-2-ylamino)-methyl]-phenol



[0168] A solution of 3,5-dibromo-pyrazin-2-ylamine (220 mg, 0.87 mmol) and 4-aminomethyl-phenol (225.0 mg, 1.83 mmol) in DMSO (2.5 mL) was heated at 98°C under nitrogen for 24 hours. HPLC showed that 35% of product was formed and 40% of starting material presented. The reaction solution was partitioned between EtOAc and water. After condensation of organic layer, the residue was purified on a silica gel column eluting with 3% methanol in dichloromethane to provide 4-[(3-amino-6-bromo-pyrazin-2-ylamino)-methyl]-phenol (30 mg) as a yellow solid.

[0169] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (s, 1H), 7.15 (s, 1H), 7.12 (d, 2H), 6.81 (t, 1H), 6.70 (d, 2H), 6.08 (s, 2H), 4.37 (d, 2H); MS (ES^+) *m/z* 297 ($M+H^+$).

Step 2: Preparation of 4-[(3-amino-6-thiophen-2-yl-pyrazin-2-ylamino)-methyl]-phenol



[0170] A mixture of 4-[(3-amino-6-bromo-pyrazin-2-ylamino)-methyl]-phenol (25 mg, 0.085 mmol), 2-thiopheneboronic acid (13 mg, 0.10 mmol), $Pd(PPh_3)_2Cl_2$ (2 mg, 0.0028 mmol), and $NaHCO_3$ (21 mg, 0.25 mmol) in DME (0.5 mL) and water (0.15 mL) was put in a microwave reaction tube and reacted in a microwave reactor at 110 °C for 7 minutes. The reaction

mixture was partitioned in ethyl acetate and water, and the organic layer was evaporated. The residue was purified on a C-18 reversed phase preparative HPLC eluting with Methanol/Acetonitrile containing 0.1% trifluoroacetic acid to 4-[(3-amino-6-thiophen-2-yl-pyrazin-2-ylamino)-methyl]-phenol trifluoroacetic acid salt as a white solid (12 mg).

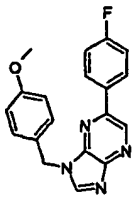
[0171] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (br s, 1H), 7.64 (s, 1H), 7.48 (d, 1H), 7.47 (d, 1H), 7.32 (s, 2H), 7.22 (d, 2H), 7.06 (t, 1H), 6.68 (d, 2H), 4.48 (s, 2H); MS (ES^+) *m/z* 299 ($M+H^+$).

Step 3: Preparation of 4-(6-thiophen-2-yl-imidazo[4,5-b]pyrazin-1-ylmethyl)-phenol

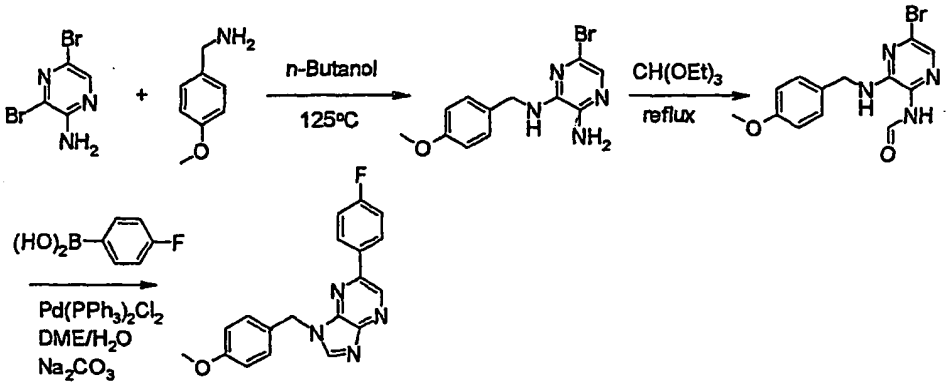
[0172] A solution of 4-[(3-amino-6-thiophen-2-yl-pyrazin-2-ylamino)-methyl]-phenol trifluoroacetic acid salt (10 mg, 0.024 mmol) in triethyl orthoformate (1.5 mL) was refluxed for 4 hours. The starting material was disappeared completely. After evaporation of triethyl orthoformate, the crude product was crystallized in hexane-dichloromethane system to provide 4-(6-thiophen-2-yl-imidazo[4,5-b]pyrazin-1-ylmethyl)-phenol as a brown solid (5 mg).

[0173] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H), 9.08 (s, 1H), 8.81 (s, 1H), 7.96 (d, 1H), 7.70 (d, 1H), 7.31 (d, 2H), 7.20 (m, 1H), 6.70 (d, 2H), 5.36 (s, 2H); MS (ES^+) *m/z* 309 ($M+H^+$).

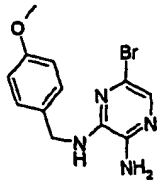
Example 2: 6-(4-Fluoro-phenyl)-1-(4-methoxy-benzyl)-1H-imidazo[4,5-b]pyrazine



Synthetic Scheme II:



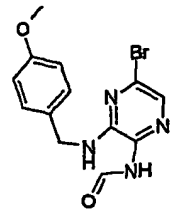
Step 1: Preparation of 5-Bromo-N-3-(4-methoxy-benzyl)-pyrazine-2,3-diamine



[0174] A solution of 3,5-dibromo-pyrazin-2-ylamine (2 g, 7.91 mmol) and 4-methoxy-benzylamine (2 mL) in n-butanol (50 mL) was refluxed for 24 hours. After condensation under vacuum, the residue was purified on a silica gel column eluting with 5% methanol in dichloromethane to provide 5-bromo-N-3-(4-methoxy-benzyl)-pyrazine-2,3-diamine (940 mg, 40% yield) as a white solid.

[0175] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25 (d, 2H), 7.16 (s, 1H), 6.89 (m, 3H), 6.18 (s, 2H), 4.39 (d, 2H), 3.72 (s, 3H) .

Step 2: Preparation of *N*-[5-bromo-3-(4-methoxy-benzylamino)-pyrazin-2-yl]-formamide



[0176] A solution of 5-bromo-N-3-(4-methoxy-benzyl)-pyrazine-2,3-diamine (660 mg, 2.13 mmol) in triethyl orthoformate (15 mL) was refluxed for 4 hours. The starting material was disappeared completely, and an intermediate product was formed. After evaporation of triethyl orthoformate, toluene (30 mL) was added, and the solution was refluxed for 18 hours. *N*-[5-Bromo-3-(4-methoxy-benzylamino)-pyrazin-2-yl]-formamide was crystallized out during evaporation of toluene solvent and obtained as a white solid (280 mg, 39% yield).

[0177] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (d, 2H), 7.54 (s, 1H), 7.34 (t, 1H), 7.26 (d, 2H), 6.81 (d, 2H), 4.41 (d, 2H), 3.74 (s, 3H); MS (ES$^-$) *m/z* 335 (M-H$^-$).

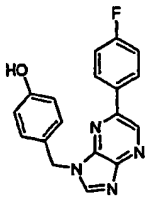
Step 3: Preparation of 6-(4-fluoro-phenyl)-1-(4-methoxy-benzyl)-1*H*-imidazo[4,5-b]pyrazine

[0178] A mixture of *N*-[5-bromo-3-(4-methoxy-benzylamino)-pyrazin-2-yl]-formamide (160 mg, 0.47 mmol), 4-fluoro-phenyl boronic acid (200 mg, 1.44 mmol), $Pd(PPh_3)_2Cl_2$ (2 mg, 0.0028 mmol), and $NaHCO_3$ (118 mg, 1.41 mmol) in DME (1 mL) and water (0.2 mL) was put in a microwave reaction tube and reacted in a microwave reactor at 110 °C for 7 minutes. The reaction mixture was partitioned in ethyl acetate and water, and the organic layer was evaporated. The residue was purified on a C-18 reversed phase preparative HPLC eluting

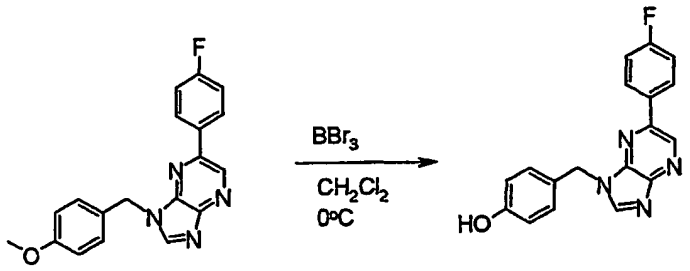
with Methanol/Acetonitrile containing 0.1% trifluoroacetic acid to provide 6-(4-fluoro-phenyl)-1-(4-methoxy-benzyl)-1*H*-imidazo[4,5-b]pyrazine as a white solid (48 mg).

[0179] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.89 (s, 1H), 8.22 (m, 2H), 7.39 (m, 4H), 6.90 (d, 2H), 5.47 (s, 2H), 3.69 (s, 3H); MS (ES^+) *m/z* 335 ($M+H^+$).

Example 3. 4-[6-(4-Fluoro-phenyl)-imidazo[4,5-b]pyrazin-1-ylmethyl]-phenol



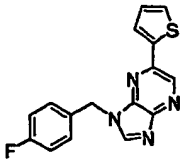
Synthetic Scheme III:



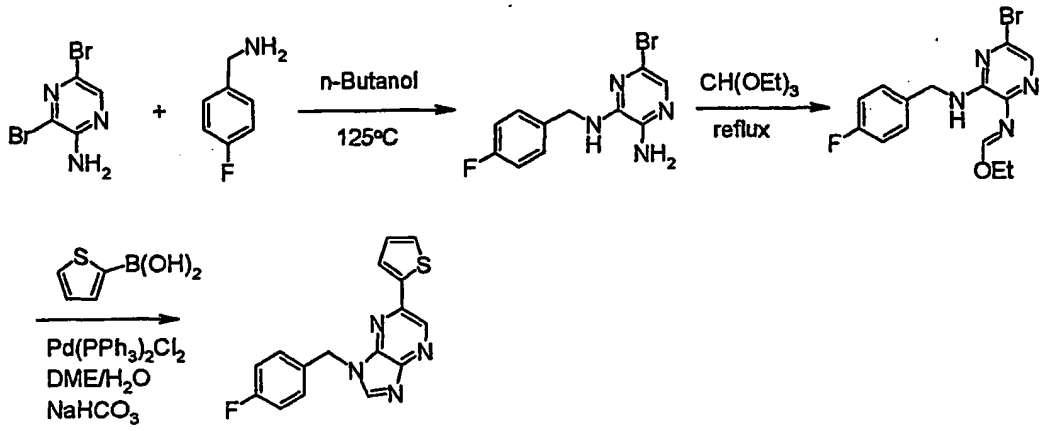
[0180] To a solution of 6-(4-fluoro-phenyl)-1-(4-methoxy-benzyl)-1*H*-imidazo[4,5-b]pyrazine (40 mg, 0.12 mmol) in anhydrous dichloromethane (3 mL) at 0°C was added BBr_3 (0.01 mL). The reaction was stirred under nitrogen at 0°C for 40 minutes, and HPLC showed the presence of 33% of starting material. Another portion of BBr_3 (0.01 mL) was added, and the reaction was continued at 0°C under nitrogen for 2 hours for the completion. The reaction solution was quenched with ice, and partitioned between dichloromethane and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified on a silica gel column eluting with EtOAc-Hexane (1:1) to provide 4-[6-(4-fluoro-phenyl)-imidazo[4,5-b]pyrazin-1-ylmethyl]-phenol as a yellow solid (34 mg).

[0181] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.96 (s, 1H), 8.32 (m, 2H), 7.60 (m, 1H), 7.43 (t, 2H), 7.35 (d, 2H), 6.77 (d, 2H), 5.48(s, 2H); MS (ES^+) *m/z* 321 ($M+H^+$).

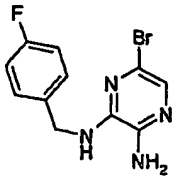
Example 4. 1-(4-Fluoro-benzyl)-6-thiophen-2-yl-1*H*-imidazo[4,5-b]pyrazine



Synthetic Scheme IV:



Step 1: Preparation of 5-bromo-N-3-(4-fluoro-benzyl)-pyrazine-2,3-diamine



[0182] A solution of 3,5-dibromo-pyrazin-2-ylamine (5 g, 19.8 mmol) and 4-fluoro-benzylamine (4.5 mL, 39.6 mmol) in n-butanol (100 mL) was refluxed for 48 hours. After condensation under vacuum, the residue was purified on a silica gel column eluting with 5% methanol in dichloromethane to provide 5-bromo-N-3-(4-fluoro-benzyl)-pyrazine-2,3-diamine (4.9 g, 83% yield) as a white solid.

[0183] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 (m, 2H), 7.15 (m, 3H), 6.98 (m, 1H), 6.18 (s, 2H), 4.47 (d, 2H).

Step 2: Preparation of 1-(4-fluoro-benzyl)-6-thiophen-2-yl-1*H*-imidazo[4,5-b]pyrazine

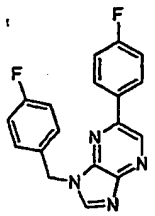
[0184] A solution of 5-bromo-N-3-(4-fluoro-benzyl)-pyrazine-2,3-diamine (2 g, 6.7 mmol) in triethyl orthoformate (50 mL) was refluxed for 14 hours. The starting material was disappeared completely, and an intermediate product was formed. After evaporation of

triethyl orthoformate, the residue was purified on a C-18 reversed phase preparative HPLC to provide the intermediate (430 mg).

[0185] A mixture of bromo intermediate(130 mg, 0.37 mmol), 2-thiopheneboronic acid (56.8 mg, 0.44 mmol), $Pd(PPh_3)_2Cl_2$ (16.5 mg, 0.023 mmol), and $NaHCO_3$ (93 mg, 1.11 mmol) in DME (2 mL) and water (0.4 mL) was put in a microwave reaction tube and reacted in a microwave reactor at 120 °C for 8 minutes. The reaction mixture was partitioned in ethyl acetate and water, and the organic layer was evaporated. The residue was purified on a C-18 reversed phase preparative HPLC eluting with Methanol/Acetonitrile containing 0.1% trifluoroacetic acid to provide 1-(4-fluoro-benzyl)-6-thiophen-2-yl-1*H*-imidazo[4,5-b]pyrazine as a white solid (70 mg).

[0186] ^1H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.85 (s, 1H), 7.93 (d, 1H), 7.68 (d, 1H), 7.49 (m, 2H), 7.18 (m, 3H), 5.49 (s, 2H) ; MS (ES^+) *m/z* 311 ($M+H^+$).

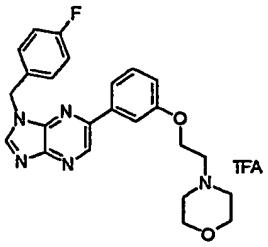
Example 5. 1-(4-Fluoro-benzyl)-6-(4-fluoro-phenyl)-1*H*-imidazo[4,5-b]pyrazine



[0187] 1-(4-Fluoro-benzyl)-6-(4-fluoro-phenyl)-1*H*-imidazo[4,5-b]pyrazine was prepared according to the same procedure as 1-(4-fluoro-benzyl)-6-thiophen-2-yl-1*H*-imidazo[4,5-b]pyrazine (Example 4).

[0188] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.92 (s, 1H), 8.22 (t, 2H), 7.52 (t, 2H), 7.38 (t, 2H), 7.18 (t, 2H), 5.55 (s, 2H) ; MS (ES^+) *m/z* 323 ($M+H^+$).

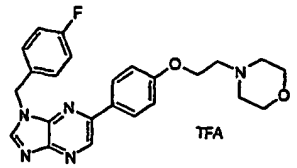
Example 6. 1-(4-Fluoro-benzyl)-6-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-1*H*-imidazo[4,5-b]pyrazine



[0189] 1-(4-Fluoro-benzyl)-6-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-1*H*-imidazo[4,5-b]pyrazine was prepared according to the same procedure as 1-(4-fluoro-benzyl)-6-thiophen-2-yl-1*H*-imidazo[4,5-b]pyrazine (Example 4).

[0190] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.94 (s, 1H), 7.81 (m, 1H), 7.72 (s, 1H), 7.48 (m, 2H), 7.16 (m, 4H), 5.58 (s, 2H), 4.46 (m, 2H), 3.97 (m, 4H), 3.58 (m, 6H) ; MS (ES^+) *m/z* 434 ($M+H^+$).

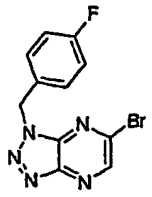
Example 7. 1-(4-Fluoro-benzyl)-6-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-1*H*-imidazo[4,5-b]pyrazine



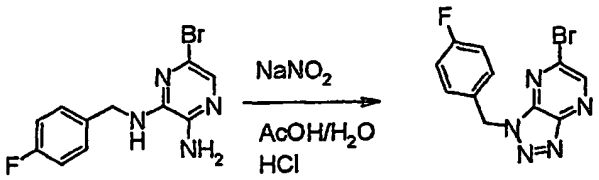
[0191] 1-(4-Fluoro-benzyl)-6-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-1*H*-imidazo[4,5-b]pyrazine was prepared according to the same procedure as 1-(4-fluoro-benzyl)-6-thiophen-2-yl-1*H*-imidazo[4,5-b]pyrazine (Example 4).

[0192] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.86 (s, 1H), 8.12 (d, 2H), 7.50 (t, 2H), 7.17 (t, 2H), 7.11 (d, 2H), 5.54 (s, 2H), 4.29 (m, 2H), 3.69 (m, 4H), 3.34 (m, 2H), 2.90 (m, 4H); MS (ES$^+$) *m/z* 434 (M+H$^+$).

Example 8. 6-Bromo-1-(4-fluoro-benzyl)-1*H*-[1,2,3]triazolo[4,5-b]pyrazine



Synthetic Scheme V:

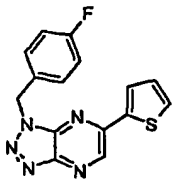


[0193] To a solution of 5-bromo-N-3-(4-fluoro-benzyl)-pyrazine-2,3-diamine (prepared in Example 4, 1.35 g, 4.5 mmol) in acetic acid (10 mL) and water (10 mL) at 0°C was added $NaNO_2$ (311 mg, 4.5 mmol) in water (1 mL) dropwisely. The reaction was stirred at 0°C for 4 hours, and HPLC showed the complete disappearance of starting material, but four new products were observed. The reaction was stirred at room temperature and then concentrated HCl (2 mL) was added. Four peaks were merged to two peaks on HPLC. All of solvents were removed, and to the residue was added acetic acid (30 mL) and concentrated HCl (70 mL). The reaction was heated at 50°C for 2 hours and then at room temperature for over night. HPLC demonstrated one major peak and two minor peaks. The reaction was

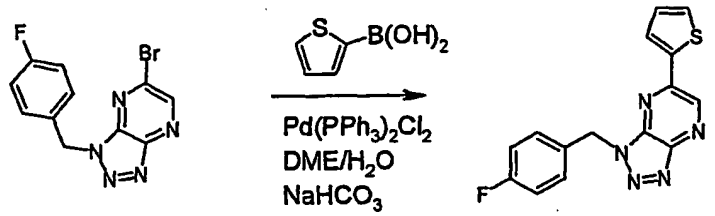
continued at 60°C for 5 hours, and HPLC showed a clean major peak. The product was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated. The residue was purified on a silica gel column to provide 6-bromo-1-(4-fluoro-benzyl)-1*H*-[1,2,3]triazolo[4,5-b]pyrazine (380 mg).

[0194] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 7.44 (m, 2H), 7.18 (t, 2H), 5.94 (s, 2H).

Example 9. 1-(4-Fluoro-benzyl)-6-thiophen-2-yl-1*H*-[1,2,3]triazolo[4,5-b]pyrazine



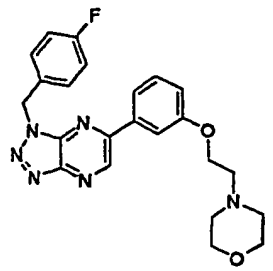
Synthetic Scheme VI:



[0195] A mixture of 6-bromo-1-(4-fluoro-benzyl)-1*H*-[1,2,3]triazolo[4,5-b]pyrazine (100 mg, 0.32 mmol), 2-thiopheneboronic acid (44.8 mg, 0.35 mmol), $Pd(PPh_3)_2Cl_2$ (11.3 mg, 0.016 mmol), and $NaHCO_3$ (80.6 mg, 0.96 mmol) in DME (2 mL) and water (0.4 mL) was put in a microwave reaction tube and reacted in a microwave reactor at 120 °C for 15 minutes. The reaction mixture was partitioned in ethyl acetate and water, and the organic layer was evaporated. The residue was purified on a silica gel column eluting with EtOAc-Hexane to provide 1-(4-fluoro-benzyl)-6-thiophen-2-yl-1*H*-[1,2,3]triazolo[4,5-b]pyrazine (18mg).

[0196] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.43 (s, 1H), 8.22 (d, 1H), 7.89 (d, 1H), 7.48 (m, 2H), 7.27 (t, 1H), 7.18 (t, 2H), 5.93 (s, 2H); MS (ES^+) *m/z* 312 ($M+H^+$).

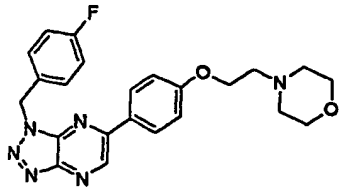
Example 10. 1-(4-Fluoro-benzyl)-6-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-1*H*-[1,2,3]triazolo[4,5-b]pyrazine



[0197] 1-(4-Fluoro-benzyl)-6-[3-(2-morpholin-4-yl-ethoxy)-phenyl]-1H-[1,2,3]triazolo[4,5-b]pyrazine was prepared according to the same procedure as 1-(4-fluoro-benzyl)-6-thiophen-2-yl-1*H*-[1,2,3]triazolo[4,5-b]pyrazine (Example 9).

[0198] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 7.83 (d, 1H), 7.81 (s, 1H), 7.51 (m, 3H), 7.18 (m, 3H), 6.02 (s, 2H), 4.21 (t, 2H), 3.58 (t, 4H), 2.78 (t, 2H), 2.53 (m, 4H); MS (ES$^+$) *m/z* 435 (M+H$^+$).

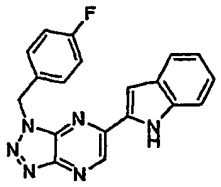
Example 11. 1-(4-Fluoro-benzyl)-6-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-1*H*-[1,2,3]triazolo[4,5-b]pyrazine



[0199] 1-(4-Fluoro-benzyl)-6-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-1*H*-[1,2,3]triazolo[4,5-b]pyrazine was prepared according to the same procedure as 1-(4-fluoro-benzyl)-6-thiophen-2-yl-1*H*-[1,2,3]triazolo[4,5-b]pyrazine (Example 9).

[0200] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.26 (d, 2H), 7.49 (m, 2H), 7.18 (m, 4H), 5.98 (s, 2H), 4.20 (t, 2H), 3.58 (t, 4H), 2.72 (t, 2H), 2.45 (m, 4H); MS (ES$^+$) *m/z* 435 (M+H$^+$).

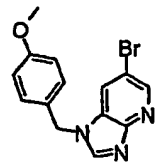
Example 12. 1-(4-Fluoro-benzyl)-6-(1*H*-indol-2-yl)-1*H*-[1,2,3]triazolo[4,5-b]pyrazine



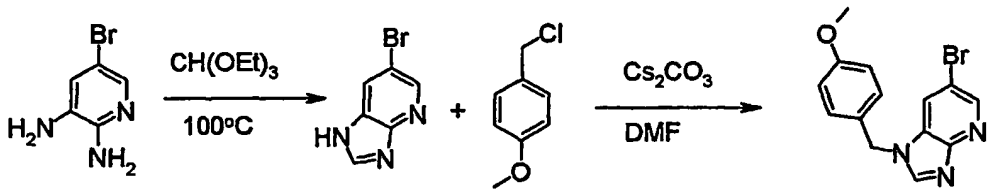
[0201] 1-(4-Fluoro-benzyl)-6-(1*H*-indol-2-yl)-1*H*-[1,2,3]triazolo[4,5-b]pyrazine was prepared according to the same procedure as 1-(4-fluoro-benzyl)-6-thiophen-2-yl-1*H*-[1,2,3]triazolo[4,5-b]pyrazine (Example 9).

[0202] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 9.48 (s, 1H), 7.68 (m, 2H), 7.55 (m, 3H), 7.23 (m, 3H), 7.05 (t, 1H), 5.97 (s, 2H); MS (ES$^+$) *m/z* 345 (M+H$^+$).

Example 13. 6-Bromo-1-(4-methoxy-benzyl)-1*H*-imidazo[4,5-b]pyridine



Synthetic Scheme VII:

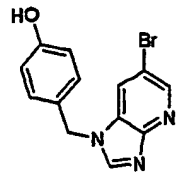


[0203] A solution of 5-bromo-pyridine-2,3-diamine (1 g, 5.3 mmol) in triethy orthoformate (40 mL) was refuxed for one hour, and TLC showed a clean product was formed. After evaporation of triethy orthoformate, a clean product 6-bromo-1*H*-imidazo[4,5-b]pyridine was obtained (1.1 g).

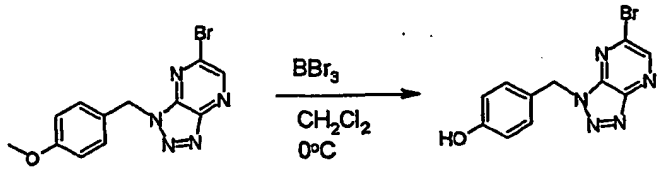
[0204] To a solution of 6-bromo-1*H*-imidazo[4,5-b]pyridine (500 mg, 2.52 mmol) and 1-chloromethyl-4-methoxy-benzene (394.6 mg, 2.52 mmol) in DMF (10 mL) was added Cs_2CO_3 (902 mg, 2.77 mmol). The reaction mixture was stirred at room temperature for 2 hours, and then partitioned between EtOAc and water. The organic layer was dried over $MgSO_4$, and concentrated. The residue was purified on a silica gel column eluting with EtOAc-Hexane to provide 6-bromo-1-(4-methoxy-benzyl)-1*H*-imidazo[4,5-b]pyridine (450 mg).

[0205] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.43 (s, 1H), 8.33 (s, 1H), 7.28 (d, 2H), 6.85 (d, 2H), 5.38 (s, 2H), 3.68 (s, 3H); MS (ES^+) *m/z* 318 ($M+H^+$).

Example 14. 4-(6-Bromo-imidazo[4,5-b]pyridin-1-ylmethyl)-phenol



Synthetic Scheme VIII:



[0206] 4-(6-Bromo-imidazo[4,5-b]pyridin-1-ylmethyl)-phenol was prepared according to the same procedure as 4-[6-(4-fluoro-phenyl)-imidazo[4,5-b]pyrazin-1-ylmethyl]-phenol (Example 3).

[0207] MS (ES^+) *m/z* 304 (MH^+).

Biological Examples

[0208] The following assays are employed to find those compounds demonstrating the optimal degree of the desired activity.

A. Assay Procedures.

[0209] The following assays may be used to determine the level of activity and effect of the different compounds of the present invention on one or more of the PKs. Similar assays can be designed along the same lines for any PK using techniques well known in the art.

[0210] Several of the assays described herein are performed in an ELISA (Enzyme-Linked Immunosorbent Sandwich Assay) format (Voller, et al., 1980, "Enzyme-Linked Immunosorbent Assay," Manual of Clinical Immunology, 2d ed., Rose and Friedman, Am. Soc. Of Microbiology, Washington, D.C., pp. 359-371). The general procedure is as follows: a compound is introduced to cells expressing the test kinase, either naturally or recombinantly, for a selected period of time after which, if the test kinase is a receptor, a ligand known to activate the receptor is added. The cells are lysed and the lysate is transferred to the wells of an ELISA plate previously coated with a specific antibody recognizing the substrate of the enzymatic phosphorylation reaction. Non-substrate components of the cell lysate are washed away and the amount of phosphorylation on the

substrate is detected with an antibody specifically recognizing phosphotyrosine compared with control cells that were not contacted with a test compound.

[0211] The presently preferred protocols for conducting the ELISA experiments for specific PKs is provided below. However, adaptation of these protocols for determining the activity of compounds against other RTKs, as well as for CTKs and STKs, is well within the scope of knowledge of those skilled in the art. Other assays described herein measure the amount of DNA made in response to activation of a test kinase, which is a general measure of a proliferative response. The general procedure for this assay is as follows: a compound is introduced to cells expressing the test kinase, either naturally or recombinantly, for a selected period of time after which, if the test kinase is a receptor, a ligand known to activate the receptor is added. After incubation at least overnight, a DNA labeling reagent such as 5-bromodeoxyuridine (BrdU) or H^3-thymidine is added. The amount of labeled DNA is detected with either an anti-BrdU antibody or by measuring radioactivity and is compared to control cells not contacted with a test compound.

MET TRANSPHOSPHORYLATION ASSAY

[0212] This assay is used to measure phosphotyrosine levels on a poly(glutamic acid:tyrosine (4:1)) substrate as a means for identifying agonists/antagonists of met transphosphorylation of the substrate.

Materials and Reagents:

1. Corning 96-well Elisa plates, Corning Catalog # 25805-96.
2. Poly(glu, tyr) 4:1, Sigma, Cat. No; P 0275.
3. PBS, Gibco Catalog # 450-1300EB
4. 50 mM HEPES
5. Blocking Buffer: Dissolve 25 g Bovine Serum Albumin, Sigma Cat. No A-7888, in 500 ml PBS, filter through a 4 μm filter.
6. Purified GST fusion protein containing the Met kinase domain, Sugen, Inc.
7. TBST Buffer.
8. 10% aqueous (MilliQue H_2O) DMSO.
9. 10 mM aqueous (dH_2O) Adenosine-5'-triphosphate, Sigma Cat. No. A-5394.
10. 2X Kinase Dilution Buffer: for 100 ml, mix 10 mL 1M HEPES at pH 7.5 with 0.4 mL 5% BSA/PBS, 0.2 mL 0.1 M sodium orthovanadate and 1 mL 5M sodium chloride in 88.4 mL dH_2O.
11. 4X ATP Reaction Mixture: for 10 mL, mix 0.4 mL 1 M manganese chloride and 0.02 mL 0.1 M ATP in 9.56 mL dH_2O.
12. 4X Negative Controls Mixture: for 10 mL, mix 0.4 mL 1 M manganese chloride in 9.6 mL dH_2O.
13. NUNC 96-well V bottom polypropylene plates, Applied Scientific Catalog # S-72092
14. 500 mM EDTA.
15. Antibody Dilution Buffer: for 100 mL, mix 10 mL 5% BSA/PBS, 0.5 mL 5% Carnation Instant Milk® in PBS and 0.1 mL 0.1 M sodium orthovanadate in 88.4 mL TBST.
16. Rabbit polyclonal antophosphotyrosine antibody, Sugen, Inc.
17. Goat anti-rabbit horseradish peroxidase conjugated antibody, Biosource, Inc.
18. ABTS Solution: for 1 L, mix 19.21 g citric acid, 35.49 g Na_2HPO_4 and 500 mg ABTS with sufficient dH_2O to make 1 L.
19. ABTS/H_2O_2: mix 15 mL ABST solution with 2μL H_2O_2 five minutes before use.
20. 0.2 M HCl

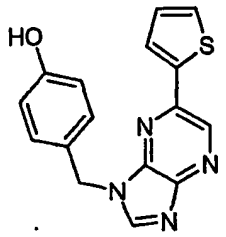
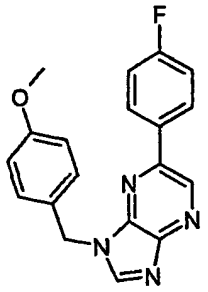
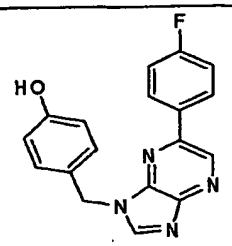
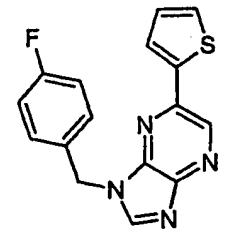
Procedure:

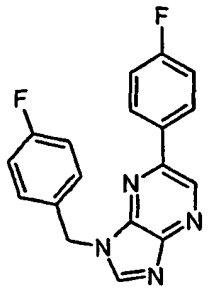
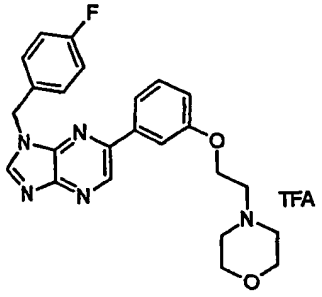
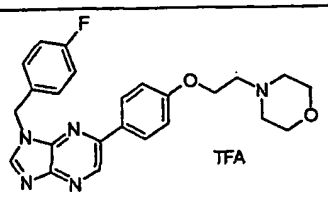
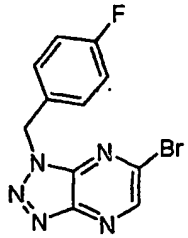
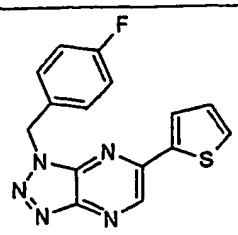
1. Coat ELISA plates with 2 µg Poly(Glu-Tyr) in 100 µL PBS, store overnight at 4 ° C.
2. Block plate with 150 µL of 5% BSA / PBS for 60 min.
3. Wash plate twice with PBS, once with 50 mM Hepes buffer pH 7.4.
4. Add 50 µl of the diluted kinase to all wells. (Purified kinase is diluted with Kinase Dilution Buffer. Final concentration should be 10 ng/well.)
5. Add 25 µL of the test compound (in 4% DMSO) or DMSO alone (4% in dH_2O) for controls to plate.
6. Incubate the kinase/compound mixture for 15 minutes.
7. Add 25 µL of 40 mM $MnCl_2$ to the negative control wells.
8. Add 25 µL ATP/ $MnCl_2$ mixture to the all other wells (except the negative controls). Incubate for 5 min.
9. Add 25 µL 500 mM EDTA to stop reaction.
10. Wash plate 3x with TBST.
11. Add 100 µL rabbit polyclonal anti-Ptyr diluted 1:10,000 in Antibody Dilution Buffer to each well. Incubate, with shaking, at room temperature for one hour.
12. Wash plate 3x with TBST.
13. Dilute Biosource HRP conjugated anti-rabbit antibody 1: 6,000 in Antibody Dilution buffer. Add 100 µL per well and incubate at room temperature, with shaking, for one hour.
14. Wash plate 1X with PBS.
15. Add 100 µl of ABTS/H_2O_2 solution to each well.
16. If necessary, stop the development reaction with the addition of 100 µl of 0.2M HCl per well.
17. Read plate on Dynatech MR7000 elisa reader with the test filter at 410 nM and the reference filter at 630 nM.

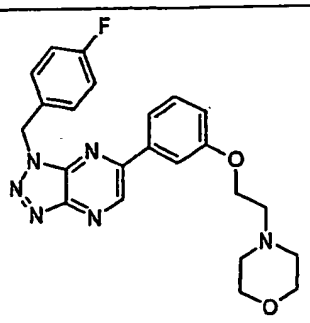
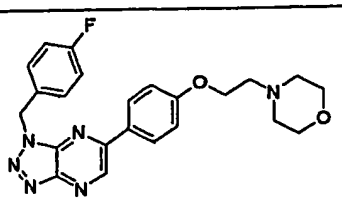
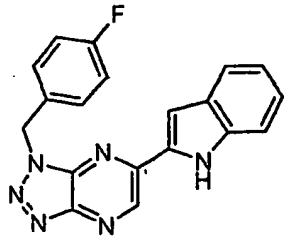
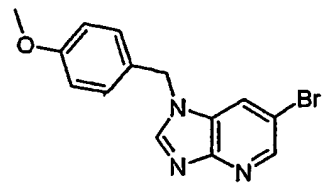
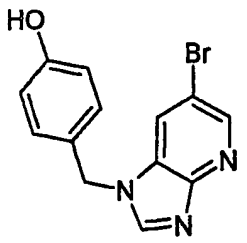
MET Transphosphorylation Assay Results:

[0213] Table 1 shows the IC_{50} values obtained for a number of compounds of the preferred embodiments of the invention.

Table 1

Compound	Example Number	c-MET IC_{50} (μM)
	1	0.15
	2	1.79
	3	0.22
	4	>20

	5	>20
	6	>20
	7	>20
	8	0.31/ 1.71
	9	0.16

	10	1
	11	0.17
	12	1.15
	13	>20
	14	9.6

[0214] One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent herein. The molecular complexes and the methods, procedures, treatments, molecules, specific compounds described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the

invention. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention are defined by the scope of the claims.

[0215] It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

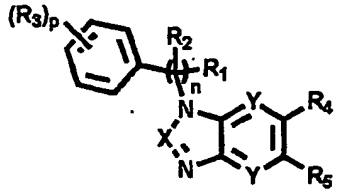
[0216] All patents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains. All patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

[0217] The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

[0218] In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group. For example, if X is described as selected from the group consisting of bromine, chlorine, and iodine, claims for X being bromine and claims for X being bromine and chlorine are fully described.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



(I)

wherein:

X is CH or N;

each Y is independently CH or N;

R_1 and R_2 are independently selected from the group consisting of hydrogen, halogen, -CN, -COR_7, -$COOR_7$, -$CONR_7R_8$, -CF_3, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl and alkynyl;

R_3 is a substituent selected from the group consisting of F, Cl, -OH, -OR_7, -COR_9, -NR_7R_8, -CN, -SO_2R_7, -$S(O)R_7$, $SO_2NR_7R_8$, -CF_3 , and lower alkyl;

wherein if p is greater than 1, then each R_3 is independently F, Cl, -OH, -OR_7, -COR_9, -NR_7R_8, -CN, -SO_2R_7, -$S(O)R_7$, $SO_2NR_7R_8$, -CF_3 , or lower alkyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, halogen, -OH, -COR_7, -$COOR_7$, -$CONR_7R_8$, -NR_7R_8, -CN, -NO_2, -$S(O)_2R_7$, -$S(O)R_7$, -$SO_2NR_6R_7$, -CF_3, -$NR_6C(O)NR_7R_8$, -$NR_6C(O)R_7$, -$NR_6SO_2R_7$ substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalicyclic, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl;

R_6, R_7 and R_8 are independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl, alkynyl, aryl, heteroaryl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl and heteroaryl; or

R_7 and R_8 or R_6 and R_7, together with the atom to which they are attached, form a heteroalicyclic ring optionally substituted with a group selected from the group consisting of alkyl, -OH, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkylamino, dialkylamino;

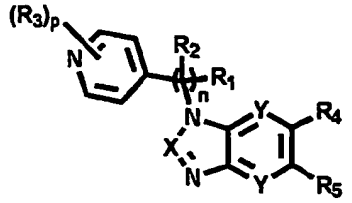
R_9 is a substituent selected from the group consisting of H, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl, alkynyl, aryl, heteroaryl, dialkylaminoalkyl, heteroaryl and alkylaminoalkyl;

n is 1, 2, or 3, it being understood that when n is greater than 1, the R_1 and R_2 groups on each carbon atom may be the same as or different from the R_1 and R_2 groups on any adjacent carbon atom; and

p is 0, 1,2, or 3; or

a pharmaceutically acceptable salt thereof.

2. A compound of the formula II:



(II)

wherein:

X is CH or N;

each Y is independently CH or N;

R_1 and R_2 are independently selected from the group consisting of hydrogen, halogen, -CN, -COR_7, -$COOR_7$, -$CONR_7R_8$, -CF_3, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl and alkynyl;

R_3 is a substituent selected from the group consisting of F, Cl, -OH, -OR_7, -COR_9, -NR_7R_8, -CN, -SO_2R_7, -S(O)R_7, $SO_2NR_7R_8$, -CF_3 , and lower alkyl;

wherein if p is greater than 1, then each R_3 is independently F, Cl, -OH, -OR_7, -COR_9, -NR_7R_8, -CN, -SO_2R_7, -S(O)R_7, $SO_2NR_7R_8$, -CF_3 , or lower alkyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, halogen, -OH, -COR_7, -$COOR_7$, -$CONR_7R_8$, -NR_7R_8, -CN, -NO_2, -$S(O)_2R_7$, -S(O)R_7, -$SO_2NR_6R_7$, -CF_3, -$NR_6C(O)NR_7R_8$, -$NR_6C(O)R_7$, -$NR_6SO_2R_7$ substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalicyclic, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl;

R_6, R_7 and R_8 are independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl, alkynyl, aryl, heteroaryl, aminoalkyl, *alkylaminoalkyl, dialkylaminoalkyl and heteroaryl; or*

R_7 and R_8 or R_6 and R_7, together with the atom to which they are attached, form a heteroalicyclic ring optionally substituted with a group selected from the group consisting of alkyl, -OH, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkylamino, dialkylamino;

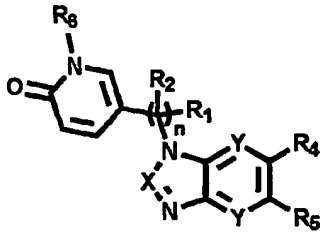
R_9 is a substituent selected from the group consisting of H, lower alkyl, cycloalkyl, *heteroalicyclic, alkenyl, alkynyl, aryl, heteroaryl, dialkylaminoalkyl, heteroaryl and* alkylaminoalkyl;

n is 1, 2, or 3, it being understood that when n is greater than 1, the R_1 and R_2 groups on each carbon atom may be the same as or different from the R_1 and R_2 groups on any adjacent carbon atom; and

p is 0, 1,2, or 3; or

a pharmaceutically acceptable salt thereof.

3. A compound of the formula III:



(III)

wherein:

X is CH or N;

each Y is independently CH or N;

R_1 and R_2 are independently selected from the group consisting of hydrogen, halogen, -CN, -COR_7, -$COOR_7$, -$CONR_7R_8$, -CF_3, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl and alkynyl;

R_3 is a substituent selected from the group consisting of F, Cl, -OH, -OR_7, -COR_9, -NR_7R_8, -CN, -SO_2R_7, -S(O)R_7, $SO_2NR_7R_8$, -CF_3 , and lower alkyl;

wherein if p is greater than 1, then each R_3 is independently F, Cl, -OH, -OR_7, -COR_9, -NR_7R_8, -CN, -SO_2R_7, -S(O)R_7, $SO_2NR_7R_8$, -CF_3 , or lower alkyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, halogen, -OH, -COR_7, -$COOR_7$, -$CONR_7R_8$, -NR_7R_8, -CN, -NO_2, -$S(O)_2R_7$, -S(O)R_7, -$SO_2NR_6R_7$, -CF_3, -$NR_6C(O)NR_7R_8$, -$NR_6C(O)R_7$, -$NR_6SO_2R_7$ substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroalicyclic, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, and substituted or unsubstituted aryl;

R_6, R_7 and R_8 are independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl, alkynyl, aryl, heteroaryl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl and heteroaryl; or

R_7 and R_8 or R_6 and R_7, together with the atom to which they are attached, form a heteroalicyclic ring optionally substituted with a group selected from the group consisting of alkyl, -OH, amino, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkylamino, dialkylamino;

R_9 is a substituent selected from the group consisting of H, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl, alkynyl, aryl, heteroaryl, dialkylaminoalkyl, heteroaryl and alkylaminoalkyl;

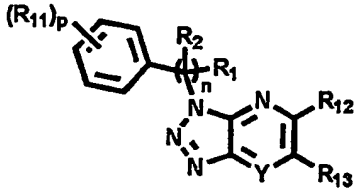
n is 1, 2, or 3, it being understood that when n is greater than 1, the R_1 and R_2 groups on each carbon atom may be the same as or different from the R_1 and R_2 groups on any adjacent carbon atom; and

p is 0, 1,2, or 3; or

a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1, 2 or 3, wherein n is 1; X is CH; Y is N; and R_3 is F, Cl or $-OR_7$.

5. A compound of the formula IV:



wherein:

p is 0, 1, 2, or 3;

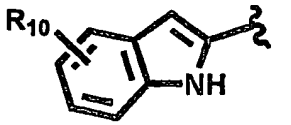
Y is CH or N;

R_1 and R_2 are independently selected from the group consisting of hydrogen, halogen, -CN, $-COR_7$, $-COOR_7$, $-CONR_7R_8$, $-CF_3$, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl and alkynyl;

each R_{11} is independently selected from the group consisting of halogen, -OH, $-OR_7$, $-COR_7$, $-COOR_7$, $-CONR_7R_8$, $-NR_7R_8$, -CN, $-NO_2$, $-S(O)_2R_7$, $-S(O)R_7$, $SO_2NR_7R_8$, $-CF_3$, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl, alkynyl and aryl;

R_{12} is selected from the group consisting of:


,

, and

,

wherein R_{10} is selected from the group consisting of hydrogen, -OH, halogen, $-O(CH_2)_mNR_7R_8$, $-NHC(O)NH(CH_2)_mNR_7R_8$, $-C(O)NR_7R_8$, $-(CH_2)_m$aryl, $-NR_6C(O)R_7$, $-NR_6SO_2R_7$, $-S(CH_2)_mNR_7R_8$, $-SO_2R_7$, $-S(O)R_7$, and $-SO_2NR_7R_8$;

wherein m is 0, 1, 2, or 3;

R_{13} is selected from the group consisting of hydrogen, halogen, $-OR_7$, $-COR_7$, $-COOR_7$, $-CONR_7R_8$, $-NR_7R_8$, -CN, $-NO_2$, $-S(O)_2R_7$, $-S(O)R_7$, $-SO_2NR_6R_7$, $-CF_3$, lower alkyl, cycloalkyl, heteroalicyclic, heteroaryl, alkenyl, alkynyl, and aryl;

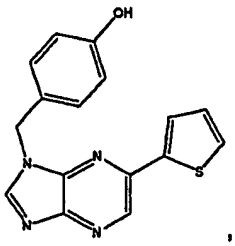
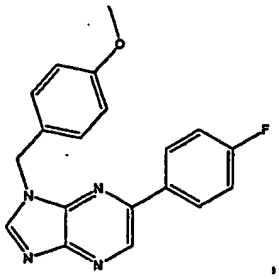
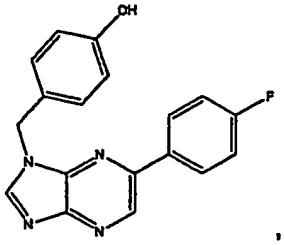
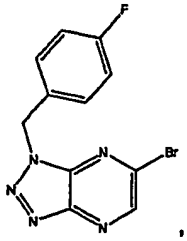
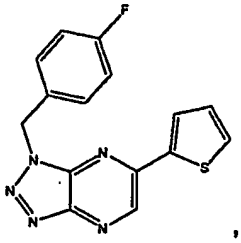
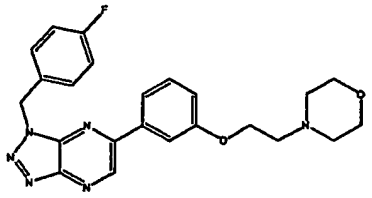
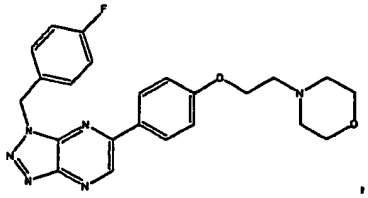
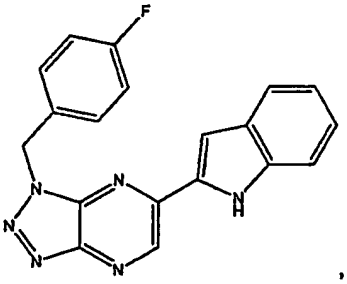
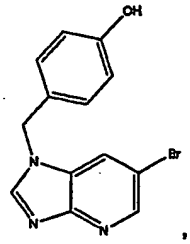
R_6, R_7 and R_8 are independently selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, heteroalicyclic, alkenyl, alkynyl, aryl, heteroaryl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl; or

R_7 and R_8 together with the atom to which they are attached form a heteroalicyclic ring optionally substituted with a group selected from the group consisting of alkyl, -OH, amino, alkylamino, dialkylamino, aminoalkyl, alkylaminoalkyl, and dialkylaminoalkyl; and

n is 1, 2, or 3, it being understood that when n is greater than 1, the R_1 and R_2 groups on each carbon atom may be the same as or different from the R_1 and R_2 groups on any adjacent carbon atom; or

a pharmaceutically acceptable salt thereof.

6. A compound selected from the group consisting of:


,

,

,

,

,

,

,

, and

,

or

a pharmaceutically acceptable salt thereof.

7. A method for treating a c-Met related disorder with a compound of any one of claims 1, 2 or 3.

8. The method of claim 7, wherein the c-Met related disorder is a cancer.

9. The method of claim 8, wherein said cancer is selected from the group consisting of breast cancer, lung cancer, colorectal cancer, prostate cancer, pancreatic cancer, glioma, liver cancer, gastric cancer, head cancer, neck cancer, melanoma, renal cancer, leukemia, myeloma, and sarcoma.

10. A pharmaceutical composition comprising a compound of any one of claims 1, 2 or 3, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.